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Appraisal of a Model for Prediction of Prognosis in Advanced Colorectal Cancer

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Previously identified prognostic factors in advanced colorectal cancer were tested in an independent population for their relationship to survival by univariate and multivariate analyses. The new population comprised 198 patients included in a randomised chemotherapy trial. The earlier identified prognostic variables were: (1) haemoglobin level (B-Hb), (2) disease-free interval, (3) Karnofsky performance status (KPS), (4) number of symptoms, and (5) whether the primary tumour was removed or not. In the new population, variables (1–3) had significant relationships to survival in both univariate and multivariate analyses, whereas variable (4) was significant only in the univariate analysis. Variable (5) was not significantly related to survival in any analysis. When a group of additional variables (white blood cell count, B-thrombocytes, S-creatinine and liver function tests) was included, S-aspartate aminotransferase (S-ASAT) was a strong predictor of survival. The independent predictive value of B-Hb, disease-free interval and KPS was confirmed in this study. S-ASAT might be an additional important prognostic factor in advanced colorectal cancer. However, the results of this study indicate that any new prognostic factor should be viewed as preliminary until verified in an independent population.

Key words: colonic neoplasms, rectal neoplasms, neoplasm metastasis, prognosis, survival rate
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INTRODUCTION

THE PROGNOSIS of patients with advanced colorectal cancer is poor, with a survival time rarely exceeding 2 years [1, 2]. Administration of 5-fluorouracil (5-FU) has been extensively used in attempts to improve the outlook, but tumour regression has been observed in less than 20% of the patients with no proven effect on survival [3, 4]. Recent studies have shown that the effect of 5-FU is enhanced by the addition of leucovorin [3, 4] or methotrexate [5]. The literature is flooded with results of new regimens based on biochemical modulation of 5-FU [3]. Knowledge of variables with impacts on prognosis is necessary in the interpretation of these trials since different distributions of prognostic variables within or between trials may influence the results.

Several patient characteristics are known to influence the prognosis of patients with advanced colorectal cancer [6–13]. Such variables are commonly derived from one population and then used for prognostic discrimination in the same population [6, 12]. This may lead to an exaggeration of the power of the prognostic model. The ultimate value of a prognostic model is, therefore, not known until the model has been tested in an independent population.

We have recently identified a group of prognostic factors in advanced colorectal cancer of which haemoglobin level (B-Hb), disease-free interval, Karnofsky performance status (KPS), number of symptoms and status of the primary tumour were the most important [14]. The present study was designed to investigate the prognostic value of these variables in an independent population, and to assess if the addition of a group of laboratory values, not recorded in the first study, would give further prognostic information.

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MATERIALS AND METHODS

Study population

All patients in this study were treated according to a protocol comparing the efficacy of sequential methotrexate/5-FU/leucovorin (MFL) to that of sequential 5-FU and leucovorin (FLv) in patients with advanced colorectal cancer (metastatic, locally recurrent or inextirpable cancer, i.e. cancer not curable by surgery or radiotherapy). This was a randomised multicentre trial in progress between January 1989 and December 1990 with the following inclusion criteria: age $\leq$ 75 years, measurable disease, symptoms from the disease, S-creatinine $<$ 125 μmol/l, S-bilirubine $<$ 40 μmol/l, no effusions, KPS $\geq$ 50 and informed consent [15]. The presence of tumour-related symptoms was evaluated at a personal interview with each patient. The MFL and FLv regimens have been described previously [15]. Of the 202 randomised patients, 4 were ineligible (2 because of S-creatinine elevation, 1 because of ascites and 1 because of lack of symptoms). The remaining 198 patients were included in the present study (Table 1).

The pretreatment patient characteristics were obtained from the trial inclusion form where all the variables in Table 1 were recorded. The first 10 variables were identical to those recorded in our previous study [14]. In the present study, white blood cell

Table 1. Characteristics of the study population

	Study population (n = 198)
Men:women	113:85
Age (years, mean, range)	63 (23–75)
KPS	
90	40
70–80	105
50–60	53
Rectum:colon	64:134
Removed primary, yes:no	165:33
No. of tumour sites (mean, range)	1.8 (1–4)
No. of symptoms (mean, range)	2.0 (1–5)
Disease-free interval*	539 (0–9997)
Haemoglobin level (g/l, mean, range)	124 (72–165)
Treatment, MFL:FLv	98:100
White blood cell count (10^9/l, mean, range)	9.0 (3.6–20.5)
B-Thrombocytes (10^9/l, mean, range)	380 (161–1200)
S-Creatinine (μmol/l, mean, range)	83 (28–195)
S-Bilirubine (μmol/l, mean, range)	10.1 (3.0–67.0)
S-Alkaline phosphatase (μcat/l, mean, range)	8.5 (1.6–50.5)
S-ASAT (μcat/l, mean, range)	0.67 (0.14–6.04)
S-ALAT (μcat/l, mean, range)	0.61 (0.07–20.5)

KPS, Karnofsky performance status; MFL, methotrexate, 5-fluorouracil, leucovorin; FLv, 5-fluorouracil, leucovorin; S-ASAT, S-aspartate aminotransferase; S-ALAT, S-alanine aminotransferase. *Interval between diagnosis of primary tumour and recurrence.

count, B-thrombocytes, S-alkaline phosphatase, S-bilirubine, S-aspartate aminotransferase (S-ASAT), S-alanine aminotransferase (S-ALAT), and S-creatinine were also collected. Survival was measured from date of randomisation to date of death of any cause. No patients were lost to follow-up. 15 patients were alive at the time of analysis with a median follow-up of 16 months (range 13–31).

Statistical methods

The relationships between explanatory variables and survival were assessed with the Cox proportional hazards model in univariate and multivariate analyses [16]. The results are presented as relative hazards (RH) with 95% confidence limits (95CL). For a categorical variable, the RH shows the hazard for an individual in a certain category compared to an individual in the reference category. For a variable in continuous form, the RH shows the effect on the hazard associated with an increase of the variable by one unit. A RH > 1.0 is associated with an increased death risk. In our previous analysis [14], the proportionality assumption connected with the Cox model was not always fulfilled, and models without assuming proportionality of the hazards over time were, therefore, also estimated, but since the results did not differ much from those obtained with the standard Cox analyses, they are not presented in this paper.

As an alternative to a full multivariate analysis, a stepwise selection procedure (inclusion criterion $P < 0.05$) was employed, and the results were used to calculate a survival score. Based on this score, the population was divided into four equally sized groups. The capability of the score to predict survival was displayed by survival curves constructed with the actuarial method. Differences between the curves were assessed with the log rank test.

Table 2. The relationship between previous variables and survival in univariate analyses

Characteristic	Present population (n = 198) RH (95CL)	Previous population (n = 340) RH (95CL)
Age	1.02 (1.00–1.03)	0.99 (0.98–1.00)
Sex	1.05 (0.78–1.41)	0.98 (0.79–1.22)
Primary rectum	0.93 (0.69–1.27)	0.76 (0.61–0.96)*
Primary unresected	0.95 (0.64–1.42)	1.53 (1.20–1.95)‡
Disease-free interval		
0	Ref.	Ref.
<365	Ref.	1.13 (0.86–1.48)
≥365	0.72 (0.54–0.96)*	0.67 (0.52–0.87)†
KPS		
100	—	Ref.
90	Ref.	1.48 (1.00–2.18)*
70–80	1.47 (0.99–2.19)	1.84 (1.32–2.56)‡
50–60	2.25 (1.44–3.51)‡	2.98 (2.09–4.25)‡
No. of symptoms	1.25 (1.07–1.46)†	1.38 (1.24–1.53)‡
No. of tumour sites	1.11 (0.90–1.37)	1.27 (1.11–1.47)‡
B-Hb (g/l)	0.985 (0.976–0.994)‡	0.978 (0.971–0.986)‡
MFL versus FLv	1.04 (0.78–1.39)	—

Ref., reference category. RH, relative hazard; 95CL, 95% confidence limits; KPS, Karnofsky performance status; B-Hb, haemoglobin levels; MFL, methotrexate, 5-fluorouracil, leucovorin; FLv, 5-fluorouracil, leucovorin. *P<0.05, †P<0.01, ‡P<0.001 (Cox proportional hazards model).

RESULTS

Previous variables

The results of the univariate and multivariate analyses are shown in Tables 2 and 3, where the RHs for the same variables derived from the previous population are also shown for comparative purposes. It can be seen that, in the present study, type of chemotherapy regimen did not influence survival, whereas age had a strong independent relationship to survival. A stepwise

Table 3. The relationship between previous variables and survival in multivariate analyses

Characteristics	Present population (n = 198) RH (95CL)	Previous population (n = 340) RH (95CL)
Age	1.033 (1.014–1.053)‡	0.993 (0.981–1.005)
Sex	0.94 (0.68–1.29)	1.09 (0.87–1.38)
Primary rectum	0.98 (0.71–1.36)	0.99 (0.77–1.26)
Primary unresected	0.67 (0.43–1.06)	1.38 (1.05–1.82)*
Disease-free interval		
<365	Ref.	Ref.
≥365	0.58 (0.42–0.81)†	0.70 (0.54–0.91)†
KPS		
100	—	Ref.
90	Ref.	0.82 (0.41–1.66)
70–80	1.38 (0.89–2.12)	0.90 (0.47–1.73)
50–60	2.00 (1.20–3.32)†	1.23 (0.59–2.56)
No. of symptoms	1.11 (0.91–1.35)	1.12 (0.95–1.32)
No. of tumour sites	1.09 (0.86–1.37)	1.11 (0.95–1.29)
B-Hb (g/l)	0.990 (0.980–0.999)*	0.982 (0.974–0.990)‡

Ref., reference category; RH, relative hazard; (95CL), 95% confidence limits; KPS, Karnofsky performance status; B-Hb, haemoglobin levels. *P<0.05, †P<0.01, ‡P<0.001 (Cox proportional hazards model).

Table 4. Previous variables with significant relation to survival in the model accepted after the stepwise selection procedure

Characteristics	Present population RH (95CL)	Previous population RH (95CL)
Age	1.027 (1.009–1.046)†	Not included
Disease-free interval		
≥365 (days)	0.65 (0.48–0.87)†	0.68 (0.53–0.88)†
KPS		
70–80	1.57 (1.04–2.35)*	Not included
50–60	2.21 (1.38–3.53)‡	1.43 (1.07–1.91)*
B-Hb (g/l)	0.988 (0.979–0.998)*	0.983 (0.975–0.990)‡
Number of symptoms	Not included	1.19 (1.05–1.35)†
Primary unresected	Not included	1.32 (1.02–1.72)*

RH, relative hazard; 95CL, 95% confidence limits; KPS, Karnofsky performance status; B-Hb, haemoglobin levels. *$P<0.05$, †$P<0.01$, ‡$P<0.001$ (Cox proportional hazards model).

selection procedure was also used to test the variables for influence on survival (Table 4). Again, age was an important variable whereas number of symptoms and treatment of the primary tumour were not accepted in the model. Disease-free interval, B-Hb and KPS were independently related to survival in the present as well as in the previous population. When the prognostic model constructed on the basis of the previous population was applied to the present one, a group with a favourable prognosis was identified (log rank, $\chi^2 = 24.0$, $P = 0.0001$), but the discrimination between the three other groups was less clear (Figure 1). If, on the other hand, the model was both constructed from and then applied to the present population, the discrimination was more distinct (log rank, $\chi^2 = 37.1, P < 0.0001$, Figure 2).

Additional variables

Almost all additional variables contained significant prognostic information in univariate analyses, but S-ASAT had the strongest relationship to prognosis (Table 5). A further univariate analysis with S-ASAT in categorised form was performed. Twenty-five per cent of the patients had S-ASAT ≤ 0.32, and this group was used as a reference category. For S-ASAT levels between 0.33 and 1.03 (percentile 25–85), the RH ranged between 0.88–1.27 with the 95CL always including 1.0. For S-ASAT levels between 1.03 and 1.99 (percentile 85–95), the RH rose to 2.59 (95CL 1.52–4.39). Finally, S-ASAT levels at or above 2.00 were connected with a RH of 20.3 (95CL 7.61–54.1). The survival in three groups according to S-ASAT level is shown in Figure 3. When the predictive value of S-ASAT was investigated separately in patients with and without hepatic

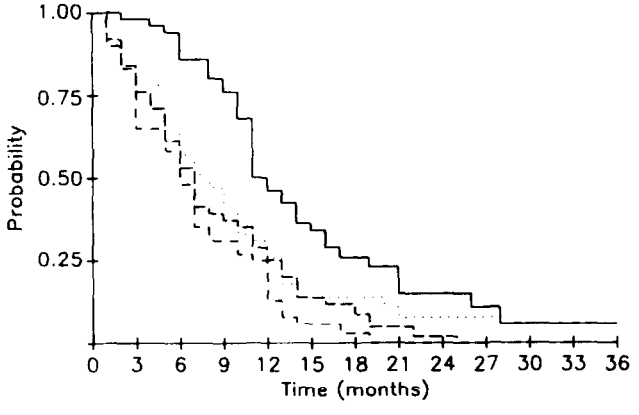

Figure 1. Survival in four groups according to prognostic index derived from the previous population: y (prognostic score) = 0.1738 (number of symptoms) − 0.0177 (B-Hb) − 0.5872 + 0.3576 (KPS ≤ 60) + 0.2795 (primary unresected) − 0.3838 (disease-free interval ≥ 365). <−2.86 (n = 50) ——, −2.86 to −2.51 (n = 51) ....., −2.50 to −2.11 (n = 49) – – –, >−2.11 (n = 48) ----.

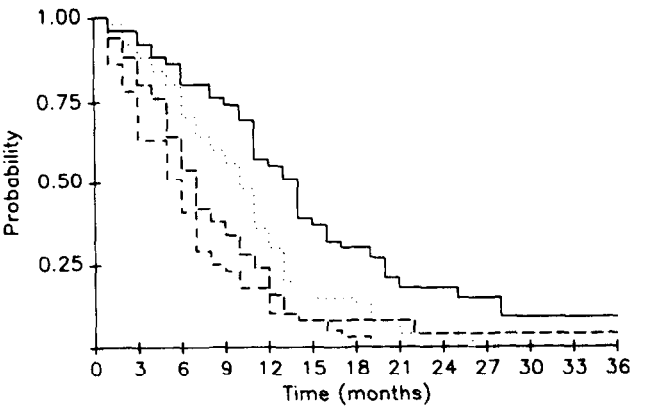

Figure 2. Survival in four groups according to prognostic index derived from the present population: y (prognostic score) = −0.0118 (B-Hb) − 0.4369 (disease-free interval ≥ 365) + 0.0270 (age) + 0.7911 (KPS ≤ 60) + 0.4477 (KPS 70–80). <0.19 (n = 49) ——, 0.19 to 0.49 (n = 50) ....., 0.50 to 0.81 (n = 50) – – –, >0.81 (n = 49) ----.

Table 5. Relationships between additional variables in continuous form and survival in univariate analyses

Variable	RH (95CL)
White blood cell count	1.076 (1.035–1.119)‡
B-Thrombocytes	1.001 (1.000–1.002)*
S-Creatinine	0.994 (0.986–1.001)
S-Bilirubine	1.024 (1.004–1.043)*
S-Alkaline phosphatase	1.047 (1.027–1.068)‡
S-ASAT	1.888 (1.527–2.335)‡
S-ALAT	1.155 (1.054–1.265)†

RH, relative hazard; (95CL), 95% confidence limits.
*$P<0.05$, †$P<0.01$, ‡$P<0.001$ (Cox proportional hazards model).

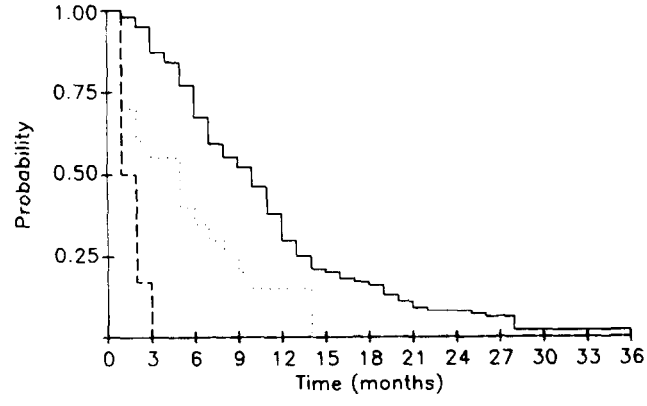

Figure 3. Survival in three groups according to S-ASAT level (μcat/l). ≤1.03 (n = 172) ——, 1.04 to 1.99 (n = 20) ....., >2.00 (n = 6) – –.

metastatases, a significant risk increase was observed in those with hepatic metastases (n = 135, RH 1.93, 95CL, 1.54–2.42, $P < 0.0001$). However, there was no obvious difference in risk between the two groups since the RH was 2.26 (95CL, 0.77–6.67, $P = 0.14$) in those without known tumour in the liver (n = 63).

The additional variables were then tested together with the former ones in a large multivariate model with 17 variables; of the additional variables, only S-ASAT (RH 1.64, 95CL 1.15–2.33, $P = 0.0013$) had independent prognostic value. In a stepwise selected model based on all variables, S-ASAT, age and white blood cell count were the most important variables followed by KPS and B-Hb (Table 6).

DISCUSSION

Three out of five variables in the final model of the previous analysis [14] had independent prognostic importance when they were tested in the present population, namely B-Hb, disease-free interval and KPS. In contrast, the independent prognostic value of the number of symptoms could not be confirmed, although this variable was significantly related to survival in univariate analysis. However, the range of exposure was smaller in this study as compared with the previous one [14] since all patients had at least one symptom. Whether the primary tumour was removed or not was not a determinant for survival in this study, maybe because only 33 (17%) patients had a persistent primary tumour. In contrast to the previous population, old age was a poor prognostic sign. Solid evidence for a predictive value of B-Hb, disease-free interval and KPS was thus obtained in this study, and these variables should, therefore, always be described in clinical trials.

The prognostic indices, in the present study as well as in the previous one, were based on stepwise selected models, where the influence of multicollinearity is reduced. When the prognostic score derived from the preceding population was applied to the present one, a fairly good prediction was observed. The impact of therapy was a potential source of error in this study since therapy (5-FU alone versus MFL) was an important determinant of prognosis in the previous population, whereas all patients in the new population were treated with equally effective drugs. Therefore, all patients were assigned the value of MFL in the analysis with the former prognostic index. Discrimination was better when both derivation and application were performed on the present population, particularly in patients with intermediate prognosis. This result indicates that if a prognostic index is derived from one population and then used for discrimination in the same population, the predictive value tends to be exaggerated. All evaluations of prognostic factors should, therefore, be regarded as preliminary until confirmed in an independent population.

This study also indicated that further prognostic information might be achieved if a group of simple laboratory values is registered before start of therapy. It is important to remember that the whole range of values for S-bilirubine and S-creatinine was not tested owing to the exclusion criteria of the trial, although a few patients were included despite elevations (Table 1). S-ASAT appeared to be a critical determinant of survival, and those with a level above 2.0 exhibited a particularly dismal prognosis. When comparing the predictive value of ASAT against the prognostic indices, it must be borne in mind that the groups in Figure 3 are not equally sized as opposed to the groups in Figures 1 and 2. Our finding that S-ASAT influences prognosis is in agreement with previous studies [13, 17, 18]. There was no evidence that the prognostic importance of S-ASAT was restricted to those with hepatic metastases, since the RH connected with S-ASAT elevation was of the same magnitude regardless of the presence of hepatic metastases, although the smaller sample size resulted in a considerably higher standard error in those without hepatic metastases. Moreover, no routine radiological examinations of the liver were performed in the absence of clinically overt disease, and the number of patients with hepatic secondaries may, therefore, have been underestimated. The independent prognostic value of S-ASAT should be verified in an independent population before its predictive value is fully known.

We conclude that B-Hb, KPS and disease-free interval are important determinants of survival in advanced colorectal cancer, but also that any prognostic factor should be verified in an independent population before its value is established.

Table 6. Final model including both previous and additional variables in a stepwise selection model

Variable	RH (95CL)
S-ASAT	1.793 (1.442–2.231)‡
Age	1.024 (1.006–1.043)†
White blood cell count	1.055 (1.013–1.100)†
KPS	0.982 (0.968–0.997)†
B-Hb	0.989 (0.980–0.998)*

RH, Relative hazard; (95CL), 95% confidence limits. *$P<0.05$, †$P<0.01$, ‡$P<0.001$ (Cox proportional hazards model).

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The Costs of Peripheral Blood Progenitor Cell Reinfusion Mobilised by Granulocyte Colony-stimulating Factor Following High Dose Melphalan as Compared with Conventional Therapy in Multiple Myeloma

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In a retrospective study, we calculated the treatment costs of 26 patients, who received either high dose melphalan combined with granulocyte colony-stimulating factor (G-CSF; filgrastim)(n=7) or without G-CSF (n=11) or alternatively, peripheral blood progenitor cell reinfusion (PBPC) mobilised by G-CSF following high dose melphalan. In comparison with the control group, a shortening of the pancytopenic period and platelet recovery was noticed in the PBPC group. This resulted in a reduction in hospital costs, diagnostics, laboratory services, total parenteral nutrition and transfusions. The average costs per treatment in the PBPC group amounted to about US$ 17 908 as compared to US$ 32 223 in the control group, implying a cost reduction of 44% when changing to PBPC reinfusion.

Key words: costs, cancer, multiple myeloma, peripheral blood stem cells, G-CSF
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INTRODUCTION

HIGH DOSE melphalan is associated with high response rates in multiple myeloma, but the treatment associated morbidity and mortality is high (about 20%, due to complications of prolonged granulocytopenia) [1,2]. Transplantations with stem cells derived either from bone marrow or from peripheral blood, and/or the administration of colony-stimulating factors are performed to hasten granulocyte recovery [3,4]. Peripheral blood progenitor cell (PBPC) transplantation is increasingly used in the treatment of malignancies to alleviate bone marrow toxicity resulting from high dose chemotherapy. It is introduced as an alternative to autologous bone marrow transplantation (ABMT) and has several advantages over ABMT, such as avoiding anaesthesia. It seems that infusion of PBPC after high dose chemotherapy is associated with markedly accelerated platelets and neutrophil recovery as compared to ABMT [4–6].

This study focuses on the costs associated with the treatment of multiple myeloma patients. The results are based on a

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