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Prognostic Variables in Patients With Advanced Colorectal Cancer Treated With Fluorouracil and Leucovorin–Based Chemotherapy

George Fountzilas, MD, Konstantinos Gossios, MD, Alkis Zisiadis, MD, Eugenia Svarna, MD, Dimosthenis Skarlos, MD, and Nicholas Pavlidis, MD

Possible prognostic variables for tumor response, time to progression (TTP), and survival in 141 patients with advanced colorectal cancer treated with fluorouracil and leucovorin–based chemotherapy were analyzed. None of the variables examined for their possible influence on tumor response attained significance in the stepwise logistic regression. In the univariate analysis, variables found to be strongly associated with TTP were performance status (PS) (P = 0.0301), liver involvement (P = 0.030), and the initial values of WBC (P = 0.0319), lactic dehydrogenase (LDH; P = 0.0053), γ-glutamyl-transpeptidase (γ-GT; P = 0.0013), alkaline phosphatase (ALP; P = 0.0186), albumin (P = 0.0004), and carcinoembryonic antigen (CEA; P =0.0014). In the Cox analysis, liver involvement (P = 0.0553), albumin (P = 0.0181), PS (P =0.0484),and ALP (P = 0.0553) were retained as independently significant variables. When only patients with liver metastases were included in the analysis, then only albumin ($P < 0.001$) demonstrated a prognostic significance. Also, in the univariate analysis, variables predicting survival were PS (P = 0.0230), grade (P = 0.0060), liver involvement (P = 0.0002), LDH (P =0.0001), γ-GT ($P < 0.001$), ALP (P = 0.0006), albumin (P = 0.0309), and CEA (P = 0.0005).With the multivariate analysis, γ-GT (P = 0.0004), albumin (P = 0.0634), and CEA (P = 0.0804) were selected as significant. In those patients who presented with liver involvement, variables predicted survival were γ-GT (P = 0.0041), albumin (P = 0.0442), and the percentage of involved liver parenchyma (P = 0.0690). These results could be helpful for the stratification of future trials in advanced colorectal cancer.

Key words: prognostic factors, colorectal cancer, chemotherapy

INTRODUCTION

Cancer of the colon and rectum is the second most common cause of cancer-related deaths in the United States. It is estimated that approximately 160,000 new cases of this cancer are discovered annually. At least 40% of them demonstrate progression during the course of their disease [1]. 5-Fluorouracil (FU) remains the single most active drug in the treatment of metastatic disease. Biochemical modulation of FU cytotoxicity has been attempted with several agents or drugs, such as folinic acid (calcium leucovorin, LV), methotrexate, interferons, and N-phosphonacetyl-L-aspartic acid (PALA) [2]. The most effective method of FU modulation appears to be combination of the drug with LV.

Significant improvements in the response rate have been observed in several randomized trials [3–10] comparing this combination with FU monotherapy, while, most importantly, a survival benefit as also seen in two of these trials [3,4]. However, despite these encouraging results, the majority of patients with advanced colorectal cancer do not respond and thus suffer only the toxicity of this treatment. Therefore, there is an obvious necessity to identify subgroups of patients who are most likely to benefit from the combination of FU and LV, in terms of either response or survival. Additionally, any information regarding the categories of prognostic factors in this patient population from several countries allows comparison of the natural history of advanced colorectal cancer in different ethnic groups. We report here on the results of an analysis of prognostic factors in a Greek population with metastatic colorectal cancer treated with chemotherapy based on the combination of FU and LV.

From the AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki (G.F., A.Z.); The "Agii Anargyri" Cancer Hospital, Athens (D.S.); and The University of Ioannina, Ioannina (K.G., E.S., N.P.), Greece.

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Address reprint requests to George Fountzilas, MD, Oncology Section, 1st Dept. of Internal Medicine, AHEPA University Hospital, 1, S. Kyriakidi str., 546 36 Thessaloniki, Greece.

TABLE I. Chemotherapeutic Regimens Used in the Two Sequential HeCOG Studies in Patients With Advanced Colorectal Cancer

Study HE 6/88 (n = 55)	Study HE 6/90 (n = 106)
FU 600 mg/m^2 weekly LV 500 mg/m^2 weekly DP 75 mg × 3 daily p.o.	FU 450 mg/m^2 weekly LV 200 mg/m^2 weekly vs. FU 450 mg/m^2 LV 200 mg/m^2 IFN-A 5 MU × 3/weekly

Fu = fluorouracil; LV = leucocorin; DP = dipyridamole; IFN-A = interferon-A.

TABLE II. Patient Characteristics

Total number	141
Age	
Range	33–78
Median	60
≤50 yr	27 (19%)
>50 yr	114 (81%)
Sex	
Male	95 (67%)
Female	47 (33%)
Performance status	
0	12 (9%)
1	74 (52%)
2	48 (34%)
3	7 (5%)
Weight loss	88 (62%)
≤10%	14 (10%)
≥10%	16 (11%)
UNK	23 (16%)
Regimen	
FU + LV	77 (55%)
FU + LV + IFN-A	32 (23%)
FU + LV + DP	32 (23%)

IFN-A = interferon-a-2b; DP = dipyridamole; UNK = unknown; see text for other abbreviations.

TABLE III. Tumor Characteristics

Primary site	
Secum/ascending	20 (14%)
Transverse	6 (4%)
Descending	7 (5%)
Sigmoid	41 (29%)
Rectum	67 (48%)
Dukes' stage	
A	5 (4%)
B	29 (21%)
C	38 (27%)
D[a]	68 (48%)
UNK	1 (0.8%)
Grade	
1	26 (18%)
2	86 (61%)
3	16 (11%)
4	5 (4%)
UNK	8 (6%)
Site of metastases	
Abdomen	25 (18%)
Pelvis	31 (22%)
Liver	89 (63%)
Ascites	10 (7%)
Nodes	28 (20%)
Lung	31 (22%)
Bone	17 (12%)

[a]Existence of metastasis at the time of initial operation.
UNK = unknown.

TABLE IV. Characteristics of Hepatic Metastases (n = 89)

Synchronous	47 (53%)
Metachronous	42 (47%)
Single	15 (17%)
Multiple	74 (83%)
Location	
Right lobe	15 (16%)
Left lobe	4 (5%)
Bilateral	70 (79%)
% of liver involvement	
≤30%	40 (45%)
>30%	49 (55%)
Calcifications	
Yes	32 (36%)
No	57 (64%)

PATIENTS AND METHODS

The hospital records of 141 patients from 3 participating centers with histologically confirmed recurrent or metastatic colorectal cancer were reviewed retrospectively. All of these patients were chemotherapy naive and were part of the patient population in two sequential studies, conducted by the Hellenic Cooperative Oncology Group (HeCOG) for Colorectal Cancer [11,12]. The chemotherapeutic regimes used in these studies were the combination of FU and LV or the combination of these two drugs with either interferon-A (IFN-A) or dipyridamole (DP) (Table I). All registered patients underwent an extensive workup before initiation of chemotherapy, which included a complete blood count, biochemistry, carcinoembryonic antigen (CEA) determination, chest x-ray, bone scan, liver scan or ultrasound, and an abdominal computed tomography (CT) scan. All the available radiological material was reevaluated by two of the authors (K.G., E.S.).

Responses were designated as follows: A complete response (CR) was defined as a complete disappearance of all clinically evident disease for at least 4 weeks. A partial response (PR) was defined as a decrease of more than 50% of the sum of the products of the largest perpendicular diameters of the measurable lesions. Stable disease (SD) was defined as an objective response without satifying the criteria of PR or an increase of less than 25% in the absence of new lesions. Progressive disease (PD)

TABLE V. Initial Laboratory Values

WBC (/mm^3)	
≤10,000	103 (73%)
>10,000	37 (26%)
UNK	1 (0.8%)
LDH (U/L)	
≤600	63 (44%)
>600	39 (28%)
UNK	39 (28%)
γ-GT (U/L)	
≤70	79 (56%)
>70	43 (30%)
UNK	19 (14%)
ALP	
Normal	73 (52%)
Abnormal	51 (36%)
UNK	17 (12%)
CEA (μg/ml)	
≤5	34 (24%)
>5	78 (55%)
UNK	29 (21%)

UNK = unknown; see text for other abbreviations.

≤600 vs. >600), alkaline phosphatase (ALP, normal vs. abnormal); γ-glutamyl-transpeptidase (γ-GT; ≤70 vs. >70), albumin (≥4 vs. <4), and CEA (≤5 vs. >5).

The cutoff point of 600 U/L for LDH in this study represented the rounded sum of the mean of all LDH values (n = 102) plus 1 SD, and it was chosen to correct for interlaboratory variations. The same applies for the cutoff points of 70 U/L for γ-GT and of 10,000/mm^3 for WBC. Also, the choice of the cutoff point of 30% of liver involvement was based on the recent literature.

Initially, in order to identify significant prognostic factors, we performed a univariate analysis of TTP and survival with each of the possible prognostic factors using the Kaplan-Meier method [13]. Survival curves were compared with the log-rank test [14]. Subsequently, those factors found significant in the univariate analysis were entered into a Cox proportional hazards regression model [15] in order to account for possible confounding. This model was reduced using a stepwise approach. The assumption of proportionality of Cox's model was checked using log minus log curves as well as Andersen's

TABLE VI. Best Response and Response by Treatment

	CR	PD	SD	PD	NE
Best response	3 (2%)	13 (9%)	33 (23%)	89 (64%)	3 (2%)
Response by treatment					
FU + LV	2 (1%)	6 (4%)	18 (13%)	50 (35%)	
FU + LV + IFN-A	0 (0%)	4 (3%)	6 (1%)	21 (15%)	
FU + LV + DP	1 (1%)	3 (2%)	9 (6%)	18 (13%)	
TOTAL	3 (2%)	13 (9%)	33 (23%)	89 (63%)	

See text for abbreviations.

was a more than 25% increase of the above-mentioned measurements or the appearance of a new lesion.

Statistical Analysis

The present analysis of the data was performed on an intention-to-treat basis, and thus, all patients, whether eligible or not and whether evaluable or not, were included. Since complete data on all factors were not available for each patient, the sample size in the analyses varied from a minimum sample size of 103 patients to a maximum of 141 patients. The prognostic factors used in the analysis for tumor response to chemotherapy, time to progression (TTP), and survival were the following: age (≤50 yr vs. >50 yr), sex (male vs. female), performance status (PS; 0–1 vs. 2–3), weight loss (none vs. ≤10% vs. >10%), primary site (colon vs. rectum), tumor grade (1–2 vs. 3–4), liver involvement (yes vs. no), regimen (FU + LV vs. FU + LV + IFN-A vs. FU + LV + DP), and the initial values of WBC (≤10.000 vs. >10.000), lactic dehydrogenase (LDH; plots [16]. Regarding collinearity among prognostic factors, we examined the significant (from the univariate analysis) continuous factors for both TTP and survival by the pairwise scatter plots and by the principal component technique [17].

Stepwise logistic regression [18] was used to identify prognostic factors significant for tumor response. All calculations were based on two-sided alternatives. All tests were carried out using the BMDP statistical package [19]. A 10% level of significance was used for variables to enter the model into the stepwise method.

Because of the relatively small sample size and the number of factors involved, the power of the study was rather limited. For example, with a probability of a 10% difference in response rates between different chemotherapy groups and a sample size of 141 patients, the power was 65%. The same comments hold for comparing survival. For example, with a median survival of 14 months for those patients with PS 0 or 1 and a median survival of 7 months for those with PS 2 or 3, the power of the study was 70% [18].

TABLE VII. Impact of Selected Variables on TTP and Survival Using Univariate Analysis (n = 141)

Variable	n	Median TTP (mo)	Significance	*P* value log rank	Median survival (mo)	Significance	*P* value log rank
Age							
≤50	27	5.90	No	0.3096	12.70	No	0.1918
>50	114	4.90			2.40		
Sex							
Male	94	5.44	No	0.2023	9.37	No	0.4310
Female	47	3.80			7.37		
PS							
0–1	86	5.54	Yes	0.0301	11.30	Yes	0.0230
2–3	55	4.03			6.65		
Weight loss							
No	88	5.01	No	0.1639	8.72	No	0.7068
≤10%	14	4.32			9.14		
>10%	16	5.96			8.98		
Primary site							
Colon	74	4.39	No	0.3132	8.09	No	0.4268
Rectum	67	5.90			10.00		
Grade							
1–2	112	5.27	No	0.3065	10.00	Yes	0.0060
3–4	21	4.39			6.49		
Liver involvement							
Yes	89	4.45	Yes	0.030	7.80	Yes	0.0002
No	52	5.90			14.80		
Regimen							
FU + LV	77	5.54	No	0.8643	9.14	No	0.8197
FU + LV + IFN-A	32	4.45			7.18		
FU + LV + DP	32	4.26			10.00		

IFN-A = interferon a-2b; DP = dipyridamole. See text for other abbreviations.

TABLE VIII. Impact of Selected Initial Laboratory Values on TTP and Survival Using Univariate Analysis (n = 141)

Variable	n	Median TTP (mo)	Significance	*P* value log rank	Median survival (mo)	Significance	*P* value log rank
WBC (/mm^3)							
≤10,000	103	5.54	Yes	0.0319	10.70	Yes	0.0003
>10,000	37	4.03			7.37		
LDH (U/L)							
≤600	63	6.00	Yes	0.0053	14.40	Yes	0.0001
>600	39	4.30			7.50		
γ-GT (U/L)							
≤70	79	6.09	Yes	0.0013	12.60	Yes	<0.001
>70	43	3.93			6.29		
ALP							
Normal	73	6.00	Yes	0.0186	11.80	Yes	0.0006
Abnormal	51	4.03			6.29		
CEA (μg/ml)							
≤5	34	6.00	Yes	0.0014	21.90	Yes	0.0005
>5	78	4.65			8.09		
Albumin (g/dl)							
≥4	81	6.00	Yes	0.0004	12.60	Yes	0.0309
<4	21	1.73			3.96		

See text for abbreviations.

RESULTS

Patient Population

The general characteristics of the 141 patients included in the present analysis are shown in Table II. There were 94 (67%) males and 47 (33%) females, with a median age of 60 years and a median PS of 1 on the ECOG scale. Seventy-seven (55%) patients were treated with the combination of leucovorin and FU, and 32 (23%) each with the above combination plus IFN-A or DP. Several important tumor characteristics and initial laboratory values that were analyzed for prognostic sig-

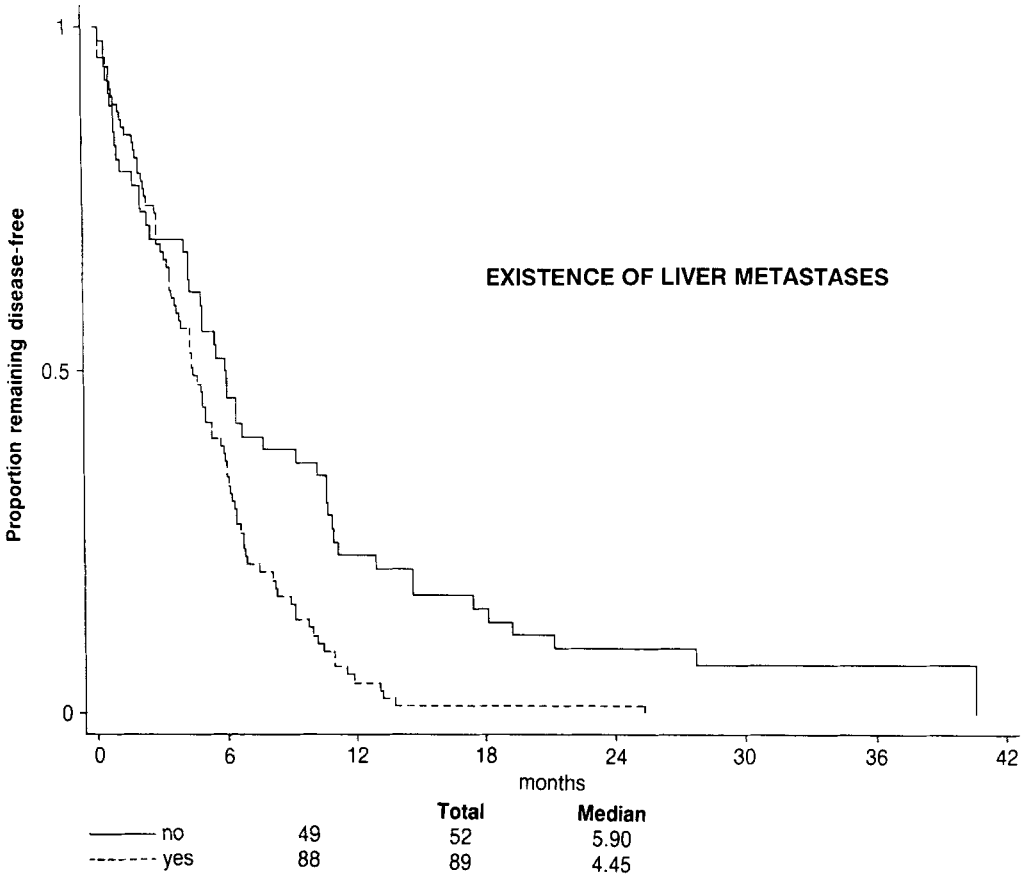

Fig. 1. Time to progression according to the existence of liver metastases (yes vs. no).

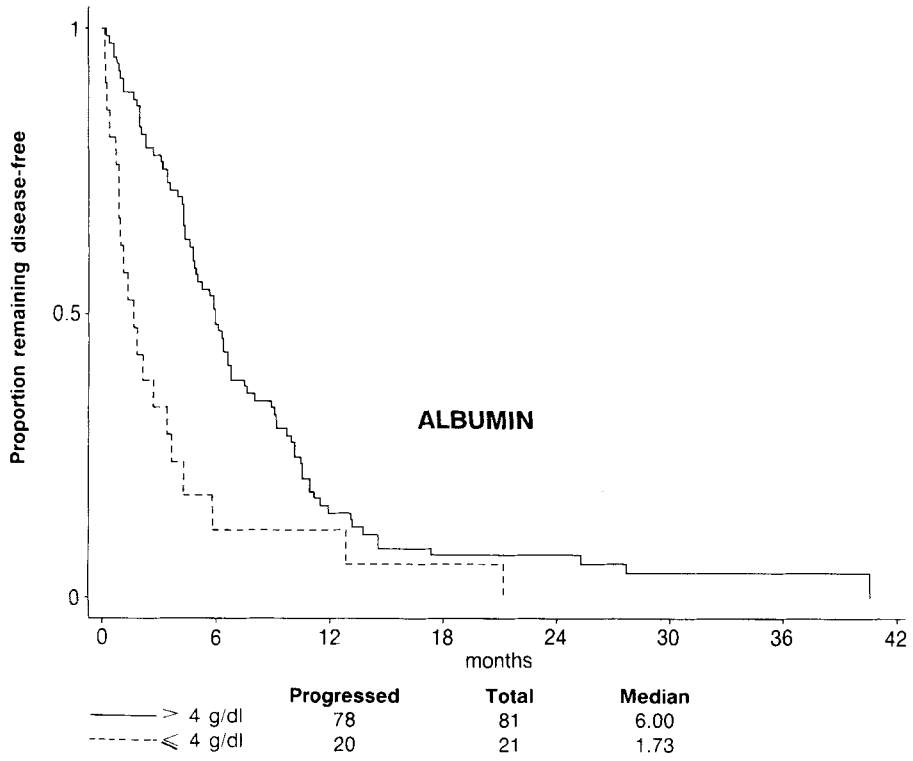

Fig. 2. Time to progression according to the initial value of albumin (≥4 g/dl vs. <4 g/dl).

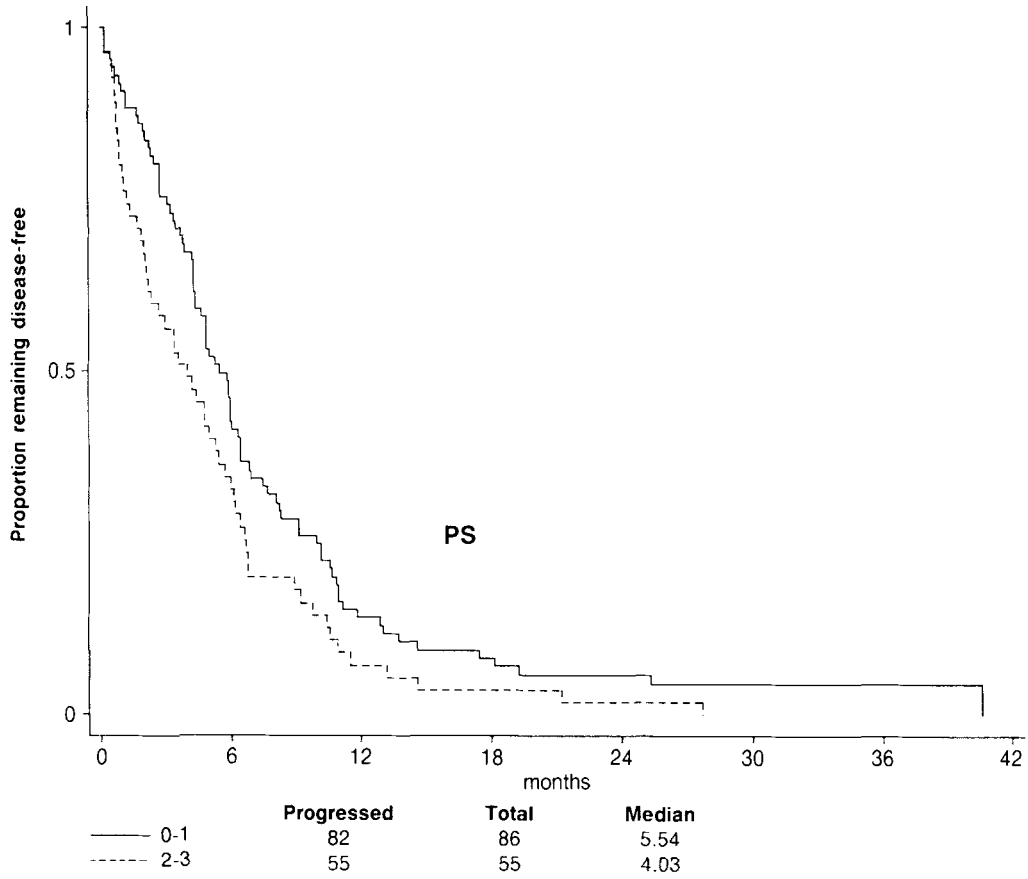

Fig. 3. Time to progression according to the initial value of PS (0–1 vs. 2–3).

nificance are presented in Tables III–V. As of September 1, 1994, after a median follow-up of 21 (range 8–53) months, 125 (89%) patients were dead.

Analysis of Tumor Response

The overall response rate and response by treatment are given in Table VI. Only 2 (2%) CRs and 13 (9%) PRs were observed. The 2 CRs lasted 27 and 37 months, respectively. The median duration of PRs was 3 (range, 1–6) months. Patients with lung metastases were also analyzed separately. Among 31 patients with lung metastases, there were only 3 (10%) PRs. Four patients with a PS of 2 demonstrated a PR. The median survival of the responding patients was 13.9 months, whereas, the survival of those with stable disease was 15.7 months. However, patients with PD had a median survival of only 6.3 months ($P = 0.0001$). None of the variables examined attained significance in the logistic regression analysis, and this may be attributed to the limited power of the study, as previously mentioned.

Prognostic Variables Influencing TTP

There were three patients who died from progressive disease, with no available information about the date of documented progression. These patients were censored, as they had progressed on the date of last follow-up. In the univariate analysis, variables found to be strongly associated with TTP were PS ($P = 0.0301$), liver involvement ($P = 0.030$), and the initial values of WBC ($P = 0.0319$), LDH ($P = 0.0053$), γ-GT ($P = 0.0013$), ALP ($P = 0.0186$), CEA ($P = 0.0014$), and albumin ($P = 0.0004$) (Tables VII and VIII, Figs. 1–4). In the Cox analysis, liver involvement ($P = 0.0177$), albumin ($P = 0.0181$), PS ($P = 0.0484$), and ALP ($P = 0.0553$) were retained as independently significant variables (Table IX).

We also performed univariate analysis only in patients with liver involvement using all the prognostic variables previously mentioned plus the location of liver metastases (right lobe, left lobe, bilateral), the number of liver metastases (single vs. multiple), and the percentage of the involved liver parenchyma (≤30% vs. 30%). In this analysis only albumin demonstrated a prognostic significance ($P < 0.001$) (Tables X and XI).

Prognostic Variables Influencing Survival

In the univariate analysis, variables predicting survival were PS ($P = 0.0230$), tumor grade ($P = 0.0060$), liver involvement ($P = 0.0002$), and the initial values ofWBC

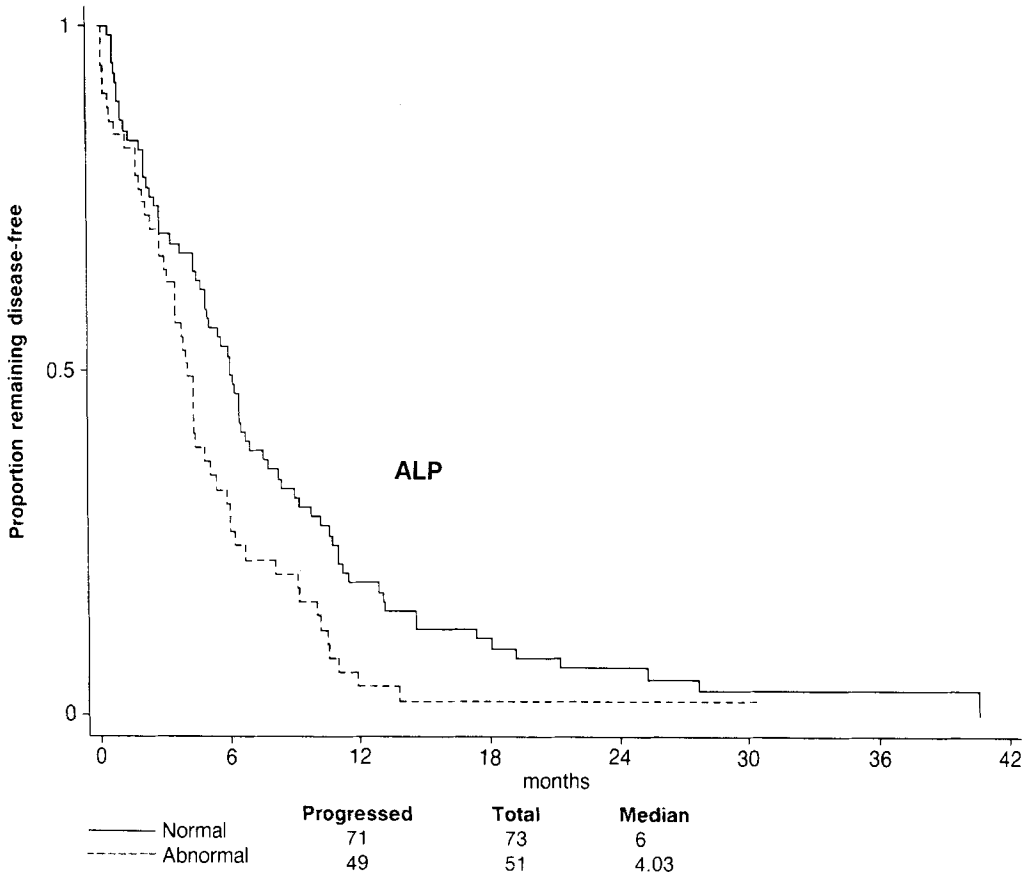

Fig. 4. Time to progression according to the initial value of ALP (normal vs. abnormal).

TABLE IX. Impact of Selected Variables on TTP Using Proportional Hazards Model*

Variable	Favorable category	Estimated hazard ratio	*P* value	Factor's impact
Liver involvement, yes vs. no	No	1.79	0.0177	−
Albumin, ≥4 vs. <4	≥4	0.55	0.0181	+
PS, <2 vs. ≥2	<2	1.56	0.0484	−
ALP, normal vs. abnormal	Normal	1.59	0.0553*	−

*Overall significance: 0.0002.
See text for abbreviations.

($P = 0.0003$), LDH ($P = 0.0001$), γ-GT ($P < 0.001$), ALP ($P = 0.0006$), CEA ($P = 0.0005$), and albumin ($P = 0.0309$) (Tables VII and VIII; Figs. 5–7). Using the Cox model, the following three variables were selected as significant: γ-GT ($P = 0.0004$), albumin ($P = 0.0634$), and CEA ($P = 0.0804$) (Table XII). Patients with a γ-GT >70 U/L were 2.66 times more likely to die from the disease than those with a value of ≤70 during the period of observation.

As with TTP, we also performed univariate analysis only in patients with liver involvement. Variables strongly associated with survival were percentage of involved liver parenchyma ($P = 0.0040$), γ-GT ($P = 0.0003$), ALP ($P = 0.0054$), albumin ($P = 0.0024$), and CEA ($P = 0.0294$) (Tables X and XI). With Cox analysis the following three variables retained their significance; γ-GT ($P = 0.0041$), albumin ($P = 0.0442$), and percentage of involved liver parenchyma ($P = 0.0690$) (Table XIII). No collinearity among prognostic factors was detected. The smallest eigenvalue of the correlation matrix of the continuous significant factors was 0.76175.

TABLE X. Impact of Selected Variables on TTP and Survival of Patients With Liver Metastases Using Univariate Analysis (n = 89)

Variable	n	Median TTP (mo)	Significance	*P* value log rank	Median survival (mo)	Significance	*P* value log rank
Age							
≤50	14	5.70	No	0.3016	8.90	No	0.4137
>50	75	4.40			7.80		
Sex							
Male	57	5.04	No	0.3292	9.01	No	0.0624
Female	32	3.47			6.36		
PS							
0–1	52	4.85	No	0.1913	8.98	No	0.2769
2–3	37	3.44			7.24		
Weight loss							
None	54	4.39	No	0.3079	7.54	No	0.9161
≤10%	13	4.32			9.14		
>10%	12	5.27			6.49		
Primary site							
Colon	54	4.32	No	0.3829	7.24	No	0.6271
Rectum	35	5.00			9.01		
Grade							
1–2	66	4.78	No	0.1842	8.98	No	0.2595
3–4	19	4.39			6.29		
Regimen							
FU + LV	52	4.39	No	0.7701	7.73	No	0.9326
F + LV + IFN-A	23	4.39			7.50		
FU + LV + DP	14	5.31			8.91		

See text for abbreviations.

TABLE XI. Impact of Selected Variables on TTP and Survival With Liver Metastases Using Univariate Analysis (n = 89)

Variable	n	Median TTP (mo)	Significance	*P* value log rank	Median survival (mo)	Significance	*P* value log rank
Location of liver metastases							
Right lobe	15	6.00	No	0.5933	10.40	No	0.5375
Left lobe	4	3.63			7.24		
Bilateral	70	4.39			7.54		
Number of liver metastases							
Single	15	6.19	No	0.3494	9.14	No	0.1930
Multiple	74	4.39			7.54		
% of liver involvement							
≤30	40	4.88	No	0.1136	6.36	Yes	0.0040
>30	49	4.32			10.70		
WBC (/mm^3)							
≤10,000	57	4.83	No	0.9641	8.98	No	0.1265
>10,000	31	4.32			7.54		
LDH (U/L)							
≤600	29	5.01	No	0.5329	10.00	No	0.0616
>600	35	4.39			7.70		
γ-GT (U/L)							
≤70	39	5.96	No	0.1077	11.80	Yes	0.0003
>70	39	3.80			6.29		
ALP							
Normal	38	4.83	No	0.1985	10.40	Yes	0.0054
Abnormal	40	3.70			4.88		
Albumin (g/dl)							
<4	13	1.83	Yes	<0.001	3.70	Yes	0.0510
≥4	50	5.04			9.04		
CEA (μg/ml)							
≤5	13	4.83	No	0.5591	14.00	Yes	0.0294
>5	58	4.63			7.80		

See text for abbreviations.

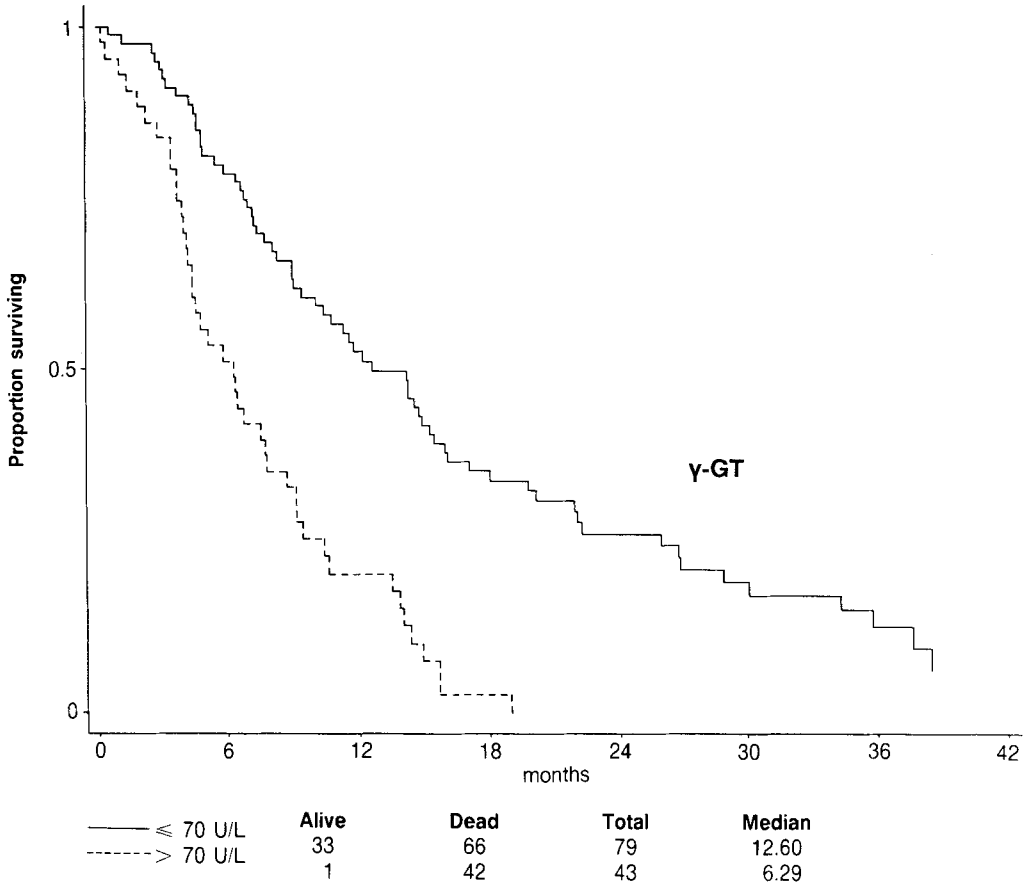

Fig. 5. Survival according to the initial value of γ-GT (≤70 U/L vs. >70 U/L).

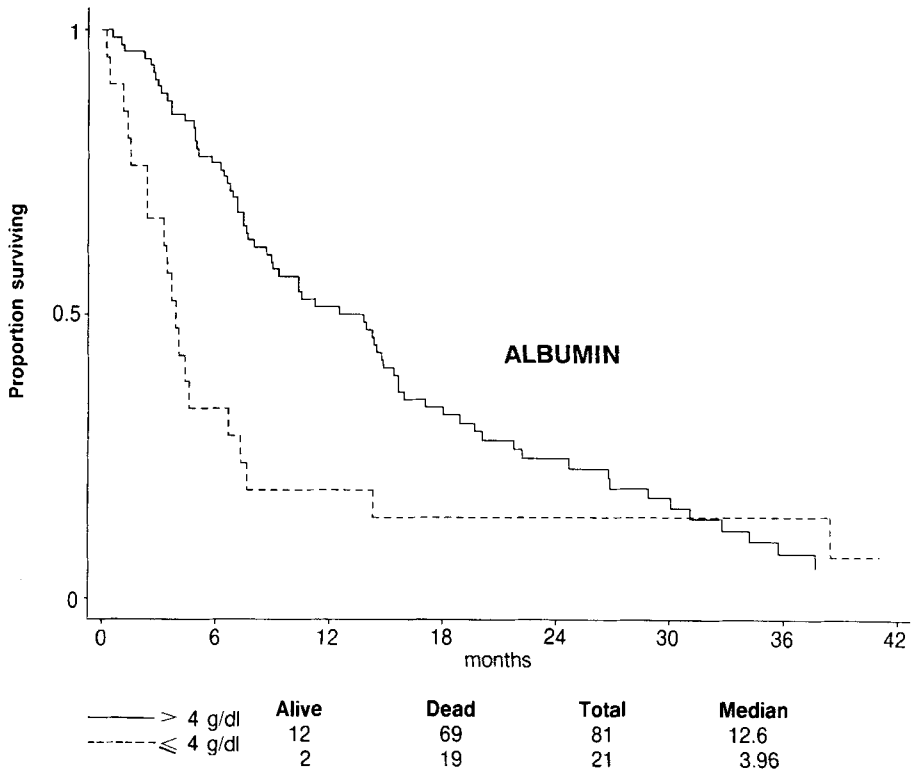

Fig. 6. Survival according to the initial value of albumin (≥4 g/dl vs. <4 g/dl).

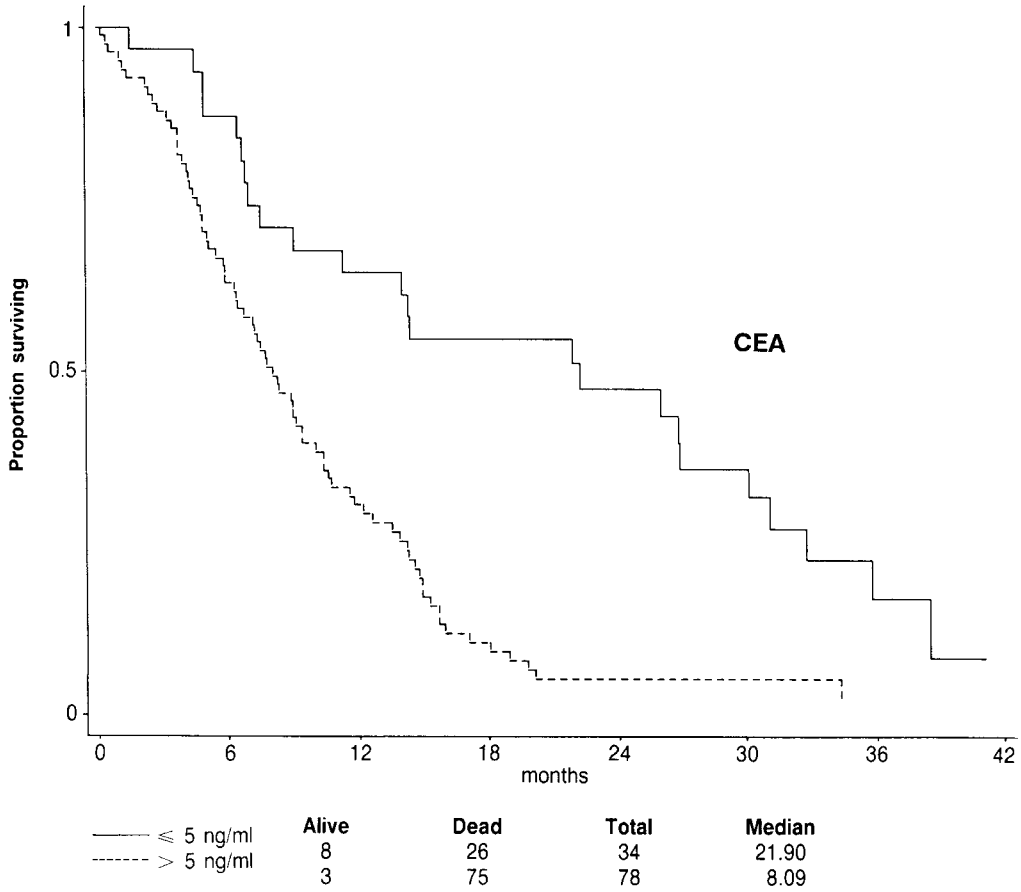

Fig. 7. Survival according to the initial value of CEA (≤5 μg/ml vs. >5 μg/ml).

TABLE XII. Impact of Selected Variables on Survival Using Proportional Hazards Model*

Variable	Favorable category	Estimated hazard ratio	*P* value	Factor's impact
γ-GT				
≤70 vs. >70	≤70	2.66	0.0004	–
Albumin				
≥4 vs. <4	≥4	0.61	0.0634*	+
CEA				
≤5 vs. >5	≤5	1.58	0.0804*	–

*Overall significance: 0.0018.

DISCUSSION

The identification of prognostic variables for response to chemotherapy and survival of patients with advanced colorectal cancer is important for the design of future clinical studies and allows for a more rational selection of subgroups of patients most likely to benefit from chemotherapy. In the present study 141 patients who entered into two sequential studies conducted by our group [11,12] were analyzed retrospectively in order to identify prognostic factors for tumor response to FU and LV–based chemotherapy (which is now considered standard treatment for this disease), time to disease progression, and survival. The patient characteristics in our study were similar to those reported in other studies from the United States and western Europe [21,22] with respect to the pattern of metastases, PS, and other variables.

By using logistic regression, we were unable to identify any variable that could significantly influence tumor response. It has been reported that the site of metastases plays a key role in determining a successful achievement of a major response to chemotherapy. For example, patients with lung metastases respond less frequently than do those with liver metastases [23]. At any rate, this was not the case in the present study, where the response rate

TABLE XIII. Impact of Selected Variables on Survival of Patients With Liver Metastases Using Proportional Hazards Model*

Variable	Favorable category	Estimated hazard ratio	*P* value	Factor's impact
γ-GT				
≤70 vs. >70	≤70	2.34	0.0041	−
Albumin				
≥4 vs. <4	≥4	0.58	0.0442	+
% of involved liver parenchyma				
≤30 vs. <30	≤30	0.58	0.0690*	+

*Overall significance: <0.001.

for lung metastases was 10%, similar to that reported by others [24]. In a meta-analysis of trials testing the modulation of combined FU and LV therapy, as compared with FU monotherapy, treatment with this combination was the only significant variable for response [25,26].

A possible explanation for our inability to identify prognostic factors influencing response might be the low (11%) response rate observed in our study. Our results are in accordance with those from other studies [27–29] but are at the lower level of the response rates observed in most recent phase III trials [6–10]. This low partial response rate among our patients could be attributed (a) to the inclusion in the present analysis of a significant number of patients with evaluable but nonmeasurable lesions, which makes it more difficult to distinguish between a PR and stabilization of the disease, (b) to the different criteria of response used by other groups as compared with those used by our radiologists (for example, in the Gastrointestinal Tumor Study Group trial a 30% reduction in hepatomegaly, measured by the sum of the measurements below the xiphoid and the costal margin at the midclavicular lines, was considered as a PR), as opposed to our earlier mentioned criteria [30], or (c) to other unidentified factors.

Using Cox analysis we found that independent prognostic factors for TTP were liver involvement, PS, albumin, and ALP; and for survival the values of γ-GT, albumin, and CEA. In a recent analysis of prognostic factors in 121 patients entered into a randomized trial comparing FU and LV with FU monotherapy, only albumin was a significant predictor for TTP [31]. It is assumed that the values of ALP or γ-GT predominantly reflect the extent of liver involvement and that those of albumin reflect the nutritional status of patients, and probably the tumor burden.

In the meta-analysis mentioned previously [25,27], PS was the only factor predicting survival, whereas in the present study PS was found to have a prognostic significance only for TTP but not for survival. This may probably be attributed to patient selection, since in most of the recently published phase III studies about 80% of the patients has a good PS, compared with the 40% of our patients demonstrating a PS of 2 or 3. Also, it should be emphasized that while in the present study all subjects received FU and LV, in the meta-analysis a large proportion of patients were treated with FU only; this influenced the response rate in most of the trials and the survival in two of them [3,4]. It is also possible that differences in the regimens used might affect the results and thus explain the lack of significance of PS in our study.

It is well known that the liver is the site most often involved with metastases in advanced colorectal cancer. There are an adequate number of published studies in which a prognostic factor analysis was performed in patients with liver metastases treated mainly with surgery only. However, we were able to identify only three studies in which patients were treated with chemotherapy, consisting of FU or FUDR, given regionally or systematically [32–34]. There are a lack of data regarding prognostic factor analysis exclusively in patients with liver metastases treated with FU and LV. Therefore, any information about the prognostic significance of any factors that affect survival would be helpful for treatment recommendations. This was the reason that in the present study we performed a Cox analysis in patients with hepatic disease. Following this analysis, γ-GT, albumin, and the percentage of involved liver parenchyma were identified as independent factors influencing survival. The extent of liver disease was found to be one of the most important prognostic factors in a number of these trials [32–43]. It appears that the percentage of involved liver parenchyma must be a stratification factor in all randomized studies evaluating different therapeutic approaches in advanced colorectal cancer.

Other significant factors influencing survival were found to be ALP [34,36,44], SGOT [44], 5′ Nt [45], LDH [24], and PS [24,38]. As was previously stated, it is believed that liver function tests reflect the extent of liver involvement, although other investigators showed that these variables were independent prognostic factors [45].

All these studies, including our own, represent a heterogeneous group of retrospective reviews of individual

institutional experiences with the treatment of advanced colorectal cancer, and thus they cannot recommend definite therapeutic guidelines. There is always a risk of discovering spurious associations with a regression analysis of multiple factors in a relatively limited number of patients, as in the present study. However, the fact that the variables identified to have prognostic significance are consistent with those already reported in the literature suggests that these variables could be useful for the stratification of patients with advanced colorectal cancer in future trials.

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