Predictors of Survival in Stage IV Metastatic Colorectal Cancer

MICHALIS ZACHARAKIS[1], IOANNIS D. XYNOS[2], ANDREAS LAZARIS[3], TSAOUSI SMARO[3], CHRISTOS KOSMAS[4], ANNA DOKOU[2], EVANGELOS FELEKOURAS[1], EFSTATHIOS ANTONIOU[5], ARIS POLYZOS[6], JOHN SARANTONIS[2], JOHN SYRIOS[3], GEORGE ZOGRAFOS[7], ALEXANDROS PAPALAMBROS[1] and NIKOLAS TSAVARIS[2]

[1]First Department of Surgery, [2]Oncology Unit, Department of Pathophysiology, [3]First Department of Pathology, [5]Second Department of Surgery – Propedeutic, and [6]Oncology Unit, First Department of Internal Medicine – Propedeutic, Laikon General Hospital, Athens University School of Medicine, Athens, Greece; [4]Second Department of Medical Oncology, Metaxa Cancer Hospital, Piraeus, Greece; [7]Department of Surgery, G. Gennimatas General Hospital, Athens, Greece

Abstract. *The aim of this study was to evaluate predictors of survival in stage IV metastatic colorectal cancer (CRC). Patients and Methods: A total of 541 patients with histologically proven metastatic CRC (UICC stage IV) were retrospectively analysed and 37 variables were tested for their potential relationship to survival. Results: Mean survival time was recorded at 12.8 months [95% confidence interval (CI) 12.0- 13.5]. Three factors were independently associated with improved survival: combination chemotherapy, improved performance status and dermatological complications. Eight factors were independently associated with unfavorable survival: worsened performance status, C-reactive protein >5 mg/dl, anemia, anorexia, weight loss ≥10%, fatigue, hypoalbuminemia and blood transfusions. Conclusion: A number of factors could be used as predictors of survival in patients with stage IV metastatic CRC. Patients who are relatively fit, have low CRP levels and tolerate combination chemotherapy appear to have a more favorable survival outcome.*

Approximately 35% of colorectal cancer (CRC) patients present with stage IV metastatic disease at the time of diagnosis and 20%-50% with stage II or III disease will progress to stage IV at some point during the course of their disease (1-3). Stage IV CRC carries a dismal prognosis: the 5-year survival rate for stage IV CRC is less than 10% (2, 3) and the median survival time of patients with stage IV CRC given optimal supportive care without chemotherapy is approximately 5 months (4).

In metastatic CRC, chemotherapy is used mainly with palliative intent. It improves quality of life and prolongs survival in comparison with best supportive care alone (4). Until a few years ago, 5-fluorouracil (5-FU) modulated with folinic acid was the reference first-line treatment option for metastatic CRC, with objective response rates of 10-25% and managable toxicity (5). Treatment options for patients with metastatic CRC are continuously evolving, with the development of new chemotherapeutic agents. With three classes of cytotoxic agents and two classes of therapeutic antibodies currently available, treatment decision-making is more complicated as the optimum sequencing and dosing of cytotoxic and biological agents remains to be determined. Nevertheless, during the past decade, the application of these new chemotherapeutic agents in the treatment of metastatic CRC has increased, with concomitant improvement in outcome (6, 7). However, as treatment with these new agents is associated with significant toxicity, there is a need to identify prognostic factors which may determine treatment response and survival. Such an approach could refine management with palliative chemotherapy according to the likelihood of clinical benefit (8). The aim of this study was to evaluate predictors of survival in stage IV metastatic CRC.

Patients and Methods

Patients. The medical records of 541 patients, with histologically proven metastatic CRC (UICC stage IV) between 1998 and 2008 were retrospectively reviewed. All were consecutive non-selected cases from a single center and all patients were treated outside of clinical trials. No patients were candidates for surgical treatment (either curative or palliative), however, all received palliative chemotherapy. Records with complete date (for the parameters used as prognostic factors) were included in the analysis. Single-agent chemotherapy regimens were based on leucovorin modulated 5-FU

Correspondence to: Nikolas Tsavaris, MD, Medical Oncology Unit, Department of Pathophysiology, Laikon General Hospital, Athens University School of Medicine, 11527 Athens, Greece. Tel: +30 2106463191, Fax: +30 2106463191, email: tsavari1@otenet.gr

Key Words: Prognostic factors, colorectal cancer, chemotherapy, survival.

(Mayo clinic or AIO regimens). Combination chemotherapy regimens included combination treatments of 5-FU (DeGrammont or simple infusion and leucovorin) with either oxaliplatin or irinotecan, or capecitabine with or without bevacizumab or cetuximab. Patients were monitored periodically for clinical and laboratory evidence of toxicity.

Prognostic variables. A total of 37 patient-related factors, tumor-related factors and complications related to either disease progression or treatment were entered in the analysis based on factors identified by previous studies (9, 10), as well as our own clinical experience. Patient-related factors included age (≤60 years or >60 years), gender and performance status (PS) according to the Karnofsky Performance Status Scale Index. Tumor-related factors included symptoms: fever (yes *vs*. no), pain (yes *vs*. no); location of metastases: lymph nodes (yes *vs*. no), liver (yes *vs*. no), lung (yes *vs*. no), abdomen/peritoneum (yes *vs*. no), pelvis (yes *vs*. no), local recurrence (yes *vs*. no), bone (yes *vs*. no), skin (yes *vs*. no), adrenal glands (yes *vs*. no); and biochemical parameters. For the latter, group categorizations were used: for carcinoembryonic antigen (CEA): normal ≤5 mg/dl and elevated >5 mg/dl; for cancer antigen 19-9 (CA 19-9): values ≤30 × normal (NL) *vs*. >30 × NL; for C reactive protein (CRP): normal <5 mg/dl, moderately elevated 5-15 mg/dl, highly elevated >15 mg/dl. Factors related to either response to treatment or disease progression included chemotherapy (single agent *vs*. combination chemotherapy), change in PS (no change, improved, worse) and hematological complications. For the latter, group categorizations were used: for neutropenia: white blood cell count >4000/μl, 2000-4000/μl, <2000/μl; for anemia: hemoglobin <8.5 g%, 8.5-10 g%, 10-12 g%, 12-13.5 g%, >13.5 g%; for thrombocytopenia: yes, platelets (PLT) ≤100,000/μl *vs*. no, PLT>100,000/μl. Other factors included nausea-vomiting (yes *vs*. no), diarrhea (absent, frequent, continuous problem), anorexia (absent, frequent, continuous problem), weight loss ≥10% (yes *vs*. no), mucositis (absent, frequent, continuous problem), fatigue (absent, frequent, continuous problem), neurological complications (yes *vs*. no), psychological complications (yes *vs*. no), alopecia (yes *vs*. no), hand and foot syndrome (yes *vs*. no), dermatological complications (yes *vs*. no), liver toxicity (yes *vs*. no), use of epoetin (yes *vs*. no), blood transfusions (yes *vs*. no) and hypoalbuminemia (yes *vs*. no).

Statistical analysis. Descriptive statistics were calculated with the use of mean, median and standard deviation for quantitative measurements and counts/percentages for discrete factors. Overall survival was defined as the time from the first day of diagnosis of metastatic CRC disease to death of any cause, or to the last follow-up examination. Survival data were studied with the use of Kaplan-Meier method. Changes in survival between groups were recorded with the log-rank test. Additionally, Wald statistics were implemented for bivariate associations between survival and quantitative measures such as age. A multivariate Cox regression model was implemented for the study of the parallel effect of remaining parameters on survival. Best model selection was based on automated techniques. Regression results were displayed in the form of regression estimates tables. Hazard ratios of outcomes under study were calculated for each parameter estimate as well as 95% confidence intervals. Categorical covariates were compared with a predefined reference category group. All analyses were conducted at a predefined significance level of 5% with the use of statistical package SPSS 12.0.

Results

Patients. A total of 541 patients were included in the study, with median age of 61.00 years (range 38 years) a mean age of 60.33 years and standard deviation of 7.35 years. The frequencies of the clinical variables are shown in Table I.

Overall survival. Survival data were collected for all patients. Based on the Kaplan-Meier method, the mean survival time was recorded at 12.8 months [95% confidence interval (CI) 12.0-13.5 months], with a median survival of 9.8 months (95% CI 8.8-10.8 months) (Figure 1).

Bivariate analysis. Improved PS, combination chemotherapy, elevated CRP, fever, pain, abdominal/peritoneal metastasis, local recurrence, anemia, anorexia, fatigue, weight loss ≥10%, thrombocytopenia, hypoalbuminemia, skin complications and blood transfusions were significantly associated with worse survival ($p<0.001$ for all, with the exception of abdominal/peritoneal metastasis, where $p=0.02$).

Multivariate analysis. Factors found to have strongest significance of a relation to survival according to the bivariate analysis were entered into the multivariate analysis model. Factors were added and excluded using the change in likelihood between models as inclusion and exclusion criteria. Forward automated procedures resulted in the final model, which is described in Table II.

Hazard ratios of risk factors. Patients with improved PS had 1.4 times lower risk of death than patients with no change of PS, while those with worsened PS had 2.6-fold higher risk of death than patients with no change in PS (Figure 2A). Patients who received combination chemotherapy had 2.6-fold lower risk of death than those who did not (Figure 2B). Probability of death increased as CRP increased; patients with CRP >15 mg/dl had 1.48-fold higher risk of death and patients with CRP 5-15 mg/dl had 1.37-fold higher risk of death than patients with CRP <5 mg/dl (Figure 2C). Anemia was also associated with higher risk of death. In particular, patients with Hb 10-12 g%, Hb 8.5-10 g% and Hb <8.5 g% had 1.58-, 1.33- and 1.38-fold respectively higher risk of death than patients with Hb >13.5 g% (Figure 2D). Patients with weight loss ≥10% had 3.3-fold higher probability of death than patients without (Figure 3A). The risk of death increased as anorexia became a more severe symptom. Patients who described anorexia as frequent problem had a 1.21-fold higher risk of death than patients without this symptom, while those patients who described anorexia as continuous problem had 2.64 times higher risk of death (Figure 3B). Similarly, the risk of death increased as fatigue became more prominent. Patients with fatigue as a frequent problem had 1.75-fold higher risk of death and patients with

Table I. *Demographic, clinical and laboratory variables in the study population (n=541).*

Factor		n	%
Gender	Males	298	55.1
	Females	243	44.9
Age	≤60 years	261	48.2
	>60 years	280	51.8
Pre- treatment PS	70	75	13.9
	80	160	29.6
	90	155	28.7
	100	151	27.9
Fever	No	459	84.5
	Yes	78	14.5
Pain	No	393	72.6
	Yes	148	27.4
CEA	≤5 mg/dl	134	24.8
	>5 mg/dl	407	75.2
CA 19-9	≤30	152	28.1
	>30	389	71.9
CRP	<5 mg/dl	405	74.9
	5-15 mg/dl	80	14.8
	>15 mg/dl	56	10.4
Metastasis			
Lymph nodes	No	351	64.9
	Yes	190	35.1
Liver	No	171	31.6
	Yes	370	68.4
Lung	No	448	82.8
	Yes	93	17.2
Peritoneal	No	300	55.5
	Yes	241	44.5
Pelvic	No	337	62.3
	Yes	204	37.7
Local recurrence	No	352	65.1
	Yes	189	34.9
Bone	No	506	93.5
	Yes	35	6.5
Skin	No	538	99.4
	Yes	3	0.6
Adrenal gland	No	540	99.8
	Yes	1	0.2
Chemotherapy	Single agent chemotherapy	244	45.1
	Combination chemotherapy	297	54.9
Change in PS	No change	218	40.3
	Improved	77	14.2
	Worse	246	45.5
Anemia	Hb >13.5 g%	198	36.6
	Hb 12-13.5 g%	94	17.4
	Hb 10-12 g%	112	20.7
	Hb 8.5-10 g%	85	15.7
	Hb <8.5 g%	52	9.6
Neutropenia	>4000/μl	42	7.7
	2000-4000/μl	62	11.5
	<2000/μl	437	80.8
Thrombocytopenia	No (PLT>100,000/μl)	389	72.4
	Yes (PLT<100,000μl)	148	27.6
Nausea – vomiting	No	294	54.3
	Yes	247	45.7
Diarrhea	Absent	249	46.3
	Frequent	188	34.9
	Continuous problem	101	18.8
Anorexia	Absent	297	54.9
	Frequent	123	22.8
	Continuous problem	121	22.4
Weight loss >10%	No	334	61.7
	Yes	207	38.3
Mucositis	Absent	313	58.1
	Frequent	139	25.8
	Continuous problem	97	16.1
Fatigue	Absent	333	61.6
	Frequent	138	25.5
	Continuous problem	70	12.9
Neurological complications	No	127	23.7
	Yes	408	76.3
Psychological complications	No	494	91.3
	Yes	47	8.7
Alopecia	No	390	72.1
	Yes	151	27.9
Hand and Foot Syndrome	No	459	84.8
	Yes	82	15.2
Dermatological Complications	No	342	63.2
	Yes	199	36.8
Liver toxicity	No	457	84.5
	Yes	84	15.5
Use of epoetin	No	468	86.5
	Yes	73	13.5
Blood transfusions	No	462	87.5
	Yes	66	12.5
Hypoalbuminemia	No	440	81.3
	Yes	101	18.7

PS, Performance status; CA 19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; WBC, white blood cells; Hb, Hemoglobin; PLTs, platelets.

fatigue as a continuous problem had 2.56-fold higher risk of death than patients not reporting this symptom (Figure 3C). Patients with dermatological complications had 1.26 times lower probability of death than did those without (Figure 3D). Patients with hypoalbuminemia had 1.27 times higher probability of death than did those without (Figure 4A) and finally the need for blood transfusions was associated with a 2-fold higher probability of death (Figure 4B).

Discussion

Over the last few years there has been an increased interest in clinical and molecular prognostic factors in stage IV metastatic CRC. One reason for this is the recent advances in treatment options which have extended patient survival. A second reason is the difference in survival for patients who receive chemotherapy in randomized trials. It is anticipated

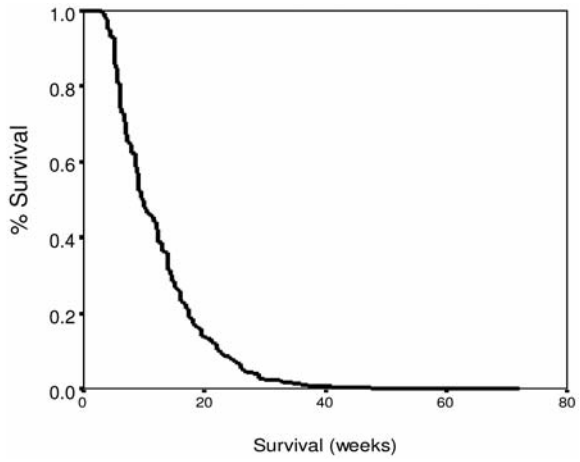

Figure 1. *Overall survival (n=541).*

that the latter could be explained by differences in patient selection and study design, since although patient stratification in randomized trials is based on selected prognostic factors such as PS, the influence of some other prognostic factors or their combination could abrogate any potential survival benefit from the antineoplastic agent or drug combination tested (10).

Our analysis included consecutive non-selected stage IV metastatic cololorectal cancer cases from a single center and all patients were treated outside of clinical trials with palliative chemotherapy only. Based on the above setting, we distinguished three groups of factors that influence survival. The first group of factors relates to clinical and laboratory parameters depicting patient functional status: worsened PS, anorexia, fatigue, weight loss, hypoalbuminemia, anemia and need for blood transfusions, which all had a negative influence on survival. On the other hand dermatological complications had a positive influence on survival. The second group of factors relates to disease burden and subsequent inflammatory response: increased CRP had negative influence on survival. The third group of factors relates to therapy: combination chemotherapy had positive influence on survival.

Various studies on survival factors for stage IV metastatic CRC have resulted in disparate results which probably depict differences in patient population and study design and hence make them difficult to evaluate. Nevertheless, in these studies PS is established as a fundamental clinical prognostic factor in metastatic CRC (11-23). Worsening PS has been definitively associated with advanced disease and poor prognosis and this is confirmed in our analysis of an unselective pool of patients with stage IV CRC. Anorexia and fatigue are commonly associated with poor general status in cancer patients and may be related to the disease itself, drug toxicity or both. Their predictive value in CRC has not been investigated before; hence, our study is the first to validate their prognostic significance in stage IV metastatic CRC. Weight loss is yet another factor associated with poor functional capability and has been shown before to be independently associated with survival in patients with advanced CRC included in irinotecan phase III trials (20).

Table II. *Final Cox proportional odds regression model.*

Variable	B	Standard error	*p*-Value	Hazard ratio	95.0% CI for hazard ratio	
					Lower	Upper
Improved PS *vs.* no change	–0.339	0.142	0.016	0.712	0.540	0.940
Worsening PS *vs.* no change	0.938	0.135	<0.001	2.555	1.961	3.329
Combination chemotherapy (yes *vs.* no)	–0.820	0.105	<0.001	0.440	0.358	0.541
CRP 5-15 mg/dl *vs.* <5 mg/dl	0.318	0.137	0.020	1.374	1.051	1.797
CRP >15 mg/dl *vs.* <5 mg/dl	0.394	0.163	0.016	1.483	1.077	2.040
Hb 12-13.5 g% *vs.* >13.5 g%	–0.021	0.146	0.885	0.979	0.736	1.303
Hb 10-12 g% *vs.* >13.5 g%	0.457	0.133	0.001	1.580	1.218	2.048
Hb 8.5–10 g% *vs.* >13.5 g%	0.291	0.145	0.044	1.338	1.007	1.777
Hb <8.5 gr% *vs.* Hb >13.5 g%	0.321	0.189	0.089	1.379	0.952	1.997
Weight loss ≥10% (yes *vs.* no)	1.200	0.120	<0.001	3.321	2.624	4.203
Anorexia (frequent *vs.* absent)	0.191	0.130	0.141	1.210	0.939	1.560
Anorexia (continuous *vs.* absent)	0.972	0.131	<0.001	2.643	2.047	3.414
Fatigue (frequent *vs.* absent)	0.562	0.126	<0.001	1.753	1.371	2.243
Fatigue (continuous *vs.* absent)	0.942	0.157	<0.001	2.566	1.885	3.493
Dermatological complications (yes *vs.* no)	–0.235	0.104	0.023	0.790	0.645	0.969
Hypoalbuminemia (yes *vs.* no)	0.243	0.121	0.044	1.274	1.006	1.614
Blood transfusions (yes *vs.* no)	0.724	0.155	<0.001	2.062	1.522	2.794

CI, Confidence interval; CRP, C reactive protein; Hb, hemoglobin.

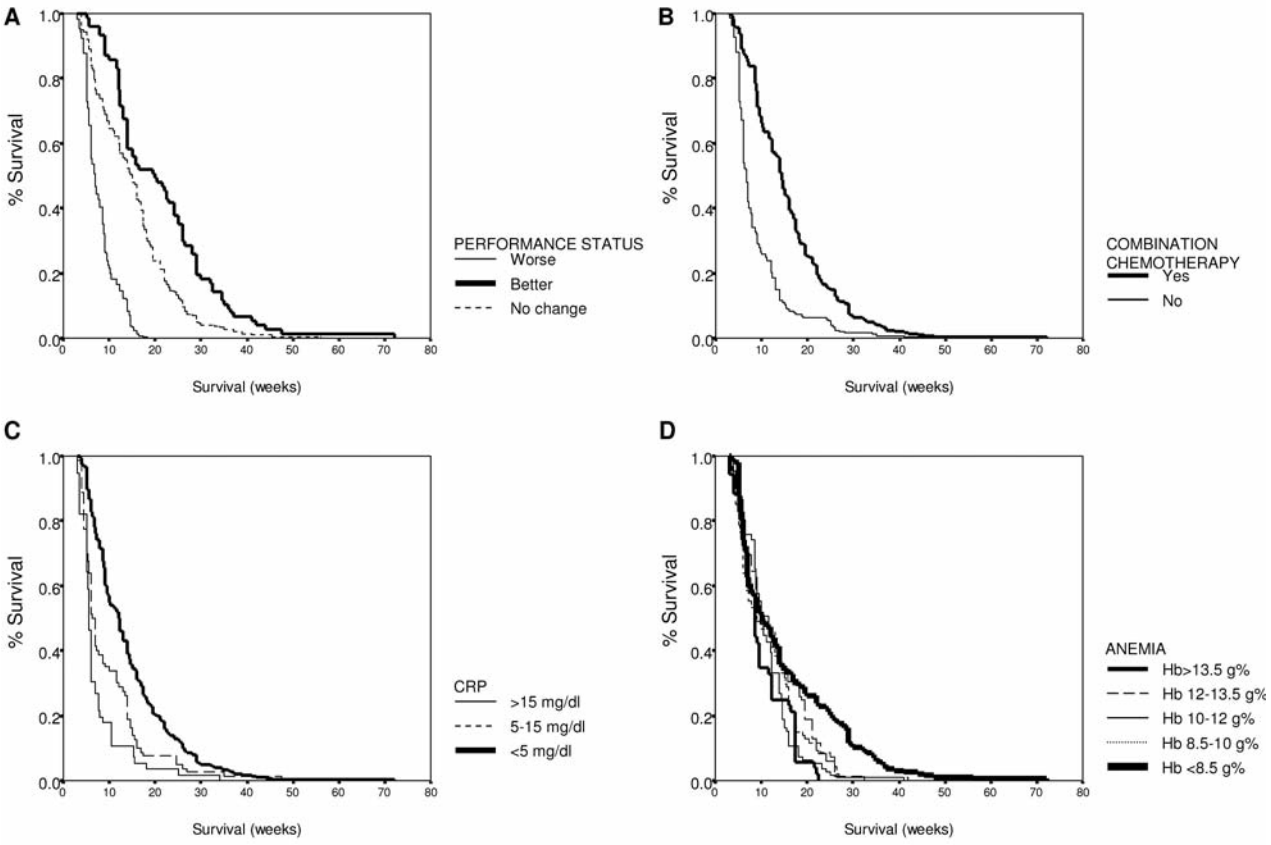

Figure 2. *Survival data according to performance status (A), combination chemotherapy (B), CRP (C) and anemia (D).*

The association between anemia and inferior survival capability has also been demonstrated by Köhne *et al*. previously in their multivariate analysis of 3,825 patients with stage IV CRC treated with palliative 5FU-based chemotherapy in the setting of 22 multinational trials (18) and the use of epoetin has been justified to reduce the need for blood transfusions (24, 25). Serum albumin reflects the nutritional status of patients, furthermore it also depicts general condition, including reserve capacity and has also been shown before to have a prognostic significance for survival in patients with metastatic CRC (12, 14, 16, 22, 26).

Skin toxicity was previously correlated to survival. In a phase II study including 346 CRC patients treated with cetuximab who were refractory to irinotecan, oxaliplatin, and fluoropyrimidines, a partial response occurred in 7%, 17%, and 20% of patients with grade 1, 2, and 3 skin rash, respectively. Survival also related strongly to the severity of the rash (27).

The role of CRP as a predictor of survival in CRC is controversial. CRP is a nonspecific but sensitive marker of inflammation. Interleukin-6 (IL-6), IL-8, and tumor necrosis factor alpha induce the synthesis of CRP in hepatocytes. CRP has been positively correlated with weight loss, anorexia-cachexia syndrome, extent of disease, and recurrence in advanced cancer including colorectal cancer (28, 29). However Wigmore *et al*. reported that there was no difference in Dukes' stage between patients with or without an elevated level of CRP (30) and Chung *et al*. performed a multivariate analysis of 172 patients with CRC and concluded that CRP level is not an independent prognostic factor for survival (31). In these studies, the prognostic significance of CRP was examined in a mixed population including patients at various stages of CRC, hence our study is the first to validate the prognostic importance of CRP for stage IV metastatic CRC.

Chemotherapy is a well established palliative treatment strategy in stage IV metastatic CRC and has been shown to independently predict survival (15, 21, 26, 32). Combination chemotherapy regimens including irinotecan and oxaliplatin in combination with 5-FU, with or without a biological agent, have improved response rates to as high as 50% and overall survival times to 15-20 months. Irinotecan-based regimens were shown to be independently associated with a better survival in patients with advanced or colorectal cancer (20, 33). Our analysis confirms the importance of combination chemotherapy as an independent predictor of survival for metastatic stage IV metastatic CRC.

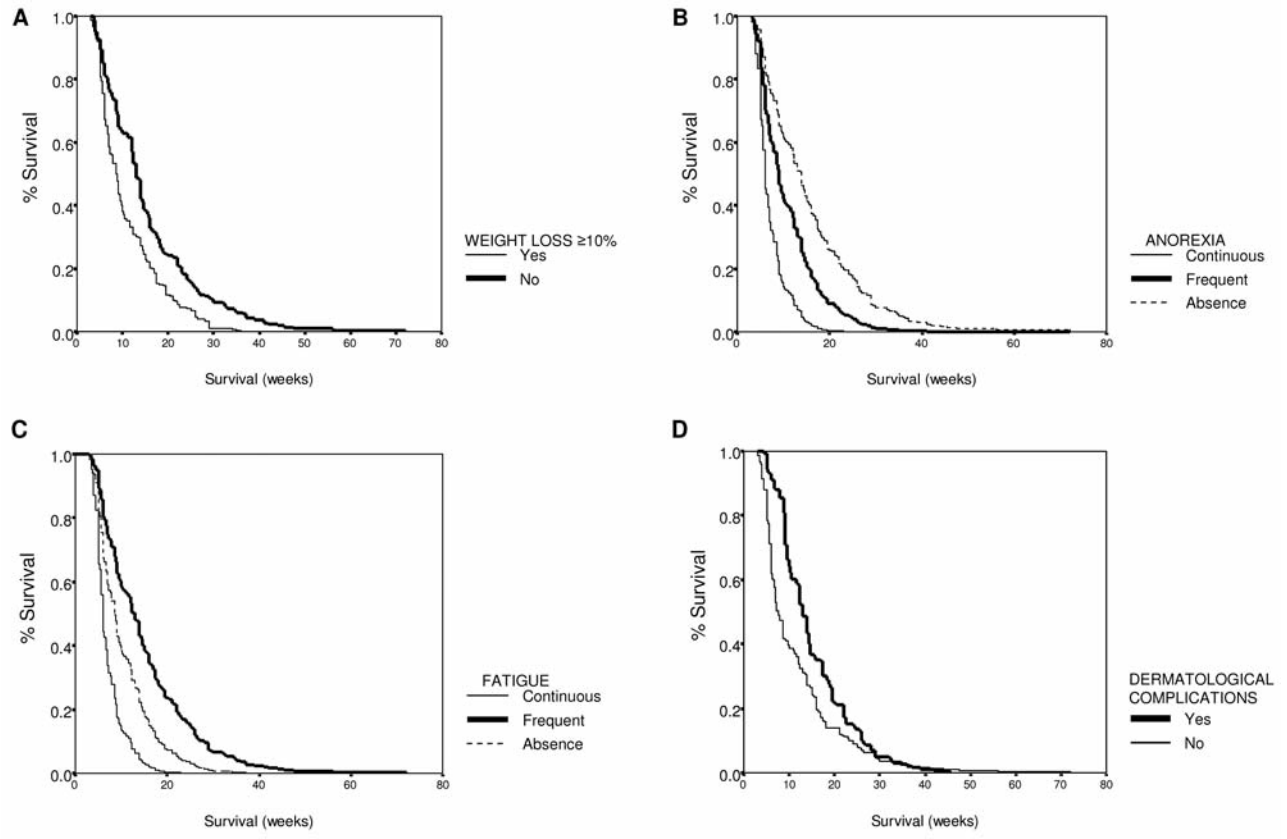

Figure 3. *Survival data according to weight loss ≥10% (A), anorexia (B), fatigue (C) and dermatological complications (D).*

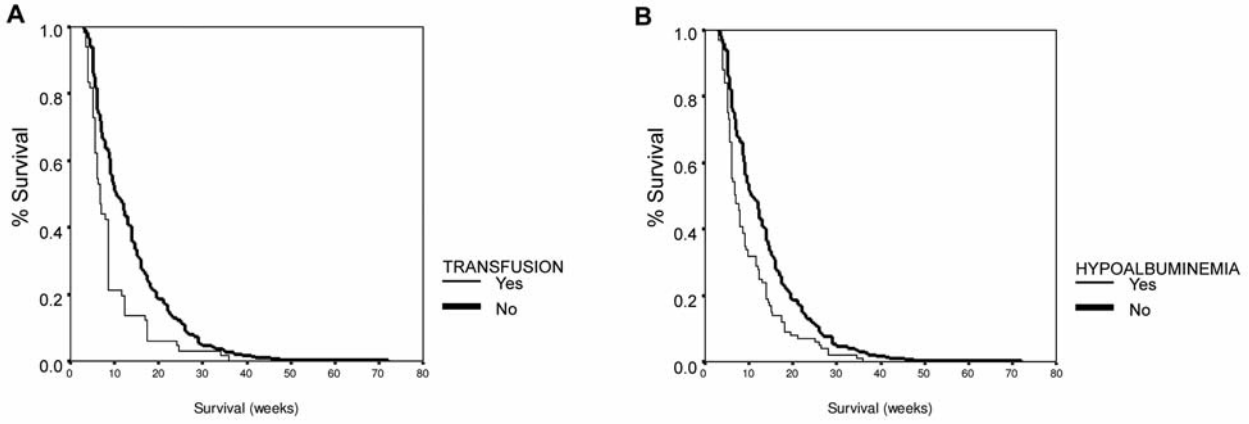

Figure 4. *Survival data according to hypoalbuminemia (A) and transfusion (B).*

In conclusion, with the present study, we define predictors of survival for patients with stage IV metastatic CRC. Patients who are relatively fit, have low CRP levels and tolerate combination chemotherapy appear to have a more favourable survival outcome. This information should be considered for the selection of appropriate management strategies for patients with stage IV metastatic CRC and the design of future clinical trials.

Acknowledgements

We thank Mrs Madalena Zlovotska for data collection and Mr Dimitrios Boulamatsis for performing the statistical tests.

References

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T and Thun MJ: Cancer statistics, 2008. CA Cancer J Clin *58*: 71-96, 2008.

2 Goldberg RM, Rothenberg ML, Van Cutsem E, Benson AB 3rd, Blanke CD, Diasio RB, Grothey A, Lenz HJ, Meropol NJ, Ramanathan RK, Becerra CH, Wickham R, Armstrong D and Viele C: The continuum of care: a paradigm for the management of metastatic colorectal cancer. Oncologist *12*: 38-50, 2007.

3 Field K and Lipton L: Metastatic colorectal cancer-past, progress and future. World J Gastroenterol *13*: 3806-3815, 2007.

4 Scheithauer W, Rosen H, Kornek GV, Sebesta C and Depisch D: Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ *306*: 752-755, 1993.

5 Folprecht G, Cunningham D, Ross P, Glimelius B, Di Costanzo F, Wils J, Scheithauer W, Rougier P, Aranda E, Hecker H and Köhne CH: Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. Ann Oncol *15*: 1330-1338, 2004.

6 Goldberg RM: Therapy for metastatic colorectal cancer. Oncologist *11*: 981-987, 2006.

7 Köhne CH and Folprecht G: Current perspectives in the treatment of metastatic colorectal cancer. Ann Oncol 15 Suppl *4*: iv43-53, 2004.

8 Pentheroudakis G, Fountzilas G, Kalofonos HP, Golfinopoulos V, Aravantinos G, Bafaloukos D, Papakostas P, Pectasides D, Christodoulou C, Syrigos K, Economopoulos T and Pavlidis N; Hellenic Cooperative Oncology Group: Palliative chemotherapy in elderly patients with common metastatic malignancies: A Hellenic Cooperative Oncology Group registry analysis of management, outcome and clinical benefit predictors. Crit Rev Oncol Hematol *66*: 237-247, 2008.

9 Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, Hammond ME, Henson DE, Hutter RV, Nagle RB, Nielsen ML, Sargent DJ, Taylor CR, Welton M and Willett C: Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med *124*: 979-994, 1999.

10 Sorbye H, Köhne CH, Sargent DJ and Glimelius B: Patient characteristics and stratification in medical treatment studies for metastatic colorectal cancer: a proposal for standardization of patient characteristic reporting and stratification. Ann Oncol *18*: 1666-1672, 2007.

11 Kemeny N and Braun DW Jr: Prognostic factors in advanced colorectal carcinoma. Importance of lactic dehydrogenase level, performance status, and white blood cell count. Am J Med *74*: 786-794, 1983.

12 Edler L, Heim ME, Quintero C, Brummer T and Queisser W: Prognostic factors of advanced colorectal cancer patients. Eur J Cancer Clin Oncol *22*: 1231-1237, 1986.

13 Graf W, Glimelius B, Påhlman L and Bergström R: Determinants of prognosis in advanced colorectal cancer. Eur J Cancer *27*: 1119-1123, 1991.

14 Steinberg J, Erlichman C, Gadalla T, Fine S and Wong A: Prognostic factors in patients with metastatic colorectal cancer receiving 5-fluorouracil and folinic acid. Eur J Cancer *28A*: 1817-1820, 1992.

15 Rougier P, Milan C, Lazorthes F, Fourtanier G, Partensky C, Baumel H and Faivre J: Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Fondation Française de Cancérologie Digestive. Br J Surg *82*: 1397-1400, 1995.

16 Assersohn L, Norman A, Cunningham D, Benepal T, Ross PJ and Oates J: Influence of metastatic site as an additional predictor for response and outcome in advanced colorectal carcinoma. Br J Cancer *79*: 1800-1805, 1999.

17 Massacesi C, Norman A, Price T, Hill M, Ross P and Cunningham D: A clinical nomogram for predicting long-term survival in advanced colorectal cancer. Eur J Cancer *36*: 2044-2052, 2000.

18 Köhne CH, Cunningham D, Di CF, Glimelius B, Blijham G, Aranda E, Scheithauer W, Rougier P, Palmer M, Wils J, Baron B, Pignatti F, Schöffski P, Micheel S and Hecker H: Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol *13*: 308-317, 2002.

19 Yuste AL, Aparicio J, Segura A, López-Tendero P, Gironés R, Pérez-Fidalgo JA, Díaz R and Calderero V: Analysis of clinical prognostic factors for survival and time to progression in patients with metastatic colorectal cancer treated with 5-fluorouracil-based chemotherapy. Clin Colorectal Cancer *2*: 231-234, 2003.

20 Mitry E, Douillard JY, Van Cutsem E, Cunningham D, Magherini E, Mery-Mignard D, Awad L and Rougier P: Predictive factors of survival in patients with advanced colorectal cancer: an individual data analysis of 602 patients included in irinotecan phase III trials. Ann Oncol *15*: 1013-1017, 2004.

21 Stelzner S, Hellmich G, Koch R and Ludwig K: Factors predicting survival in stage IV colorectal carcinoma patients after palliative treatment: a multivariate analysis. J Surg Oncol *89*: 211-217, 2005.

22 Díaz R, Aparicio J, Gironés R, Molina J, Palomar L, Segura A and Montalar J: Analysis of prognostic factors and applicability of Kohne's prognostic groups in patients with metastatic colorectal cancer treated with first-line irinotecan or oxaliplatin-based chemotherapy. Clin Colorectal Cancer *5*: 197-202, 2005.

23 Suenaga M, Mizunuma N, Shouji D, Shinozaki E, Matsusaka S, Chin K, Oya M, Yamaguchi T, Muto T and Hatake K: Modified irinotecan plus bolus 5-fluorouracil/L-leucovorin for metastatic colorectal cancer at a single institution in Japan. J Gastroenterol *43*: 842-848, 2008.

24 Glimelius B, Linné T, Hoffman K, Larsson L, Svensson JH, Näsman P, Svensson B and Helmers C: Epoetin beta in the treatment of anemia in patients with advanced gastrointestinal cancer. J Clin Oncol *16*: 434-440, 1998.

25 Chu E, Einhorn LH and Lefebvre P: Clinical benefits of once-weekly epoetin alfa in anemic patients with colorectal cancer receiving chemotherapy. J Support Oncol *4*: 243-250, 2006.

26 Lahr CJ, Soong SJ, Cloud G, Smith JW, Urist MM and Balch CM: A multifactorial analysis of prognostic factors in patients with liver metastases from colorectal carcinoma. J Clin Oncol *1*: 720-726, 1983.

27 Lenz HJ, Van Cutsem E, Khambata-Ford S, Mayer RJ, Gold P, Stella P, Mirtsching B, Cohn AL, Pippas AW, Azarnia N, Tsuchihashi Z, Mauro DJ and Rowinsky EK: Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. J Clin Oncol *24*: 4914-4921, 2006.

28 Nozoe T, Matsumata T, Kitamura M and Sugimachi K: Significance of preoperative elevation of serum C-reactive protein as an indicator for prognosis in colorectal cancer. Am J Surg *176*: 335-338, 1998.

29 McMillan DC, Wotherspoon HA, Fearon KC, Sturgeon C, Cooke TG and McArdle CS: A prospective study of tumor recurrence and the acute-phase response after apparently curative colorectal cancer surgery. Am J Surg *170*: 319-322, 1995.

30 Wigmore SJ, McMahon AJ, Sturgeon CM and Fearon KC: Acute-phase protein response, survival and tumour recurrence in patients with colorectal cancer. Br J Surg *88*: 255-260, 2001.

31 Chung YC and Chang YF: Serum C-reactive protein correlates with survival in colorectal cancer patients but is not an independent prognostic indicator. J Surg Oncol *83*: 222-226, 2003.

32 Yun HR, Lee WY, Lee WS, Cho YB, Yun SH and Chun HK: The prognostic factors of stage IV colorectal cancer and assessment of proper treatment according to the patient's status. Int J Colorectal Dis *22*: 1301-1310, 2007.

33 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L and Rougier P: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet *355*: 1041-1047, 2000.

Received August 2, 2009
Revised January 20, 2010
Accepted January 21, 2010