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A clinical nomogram for predicting long-term survival in advanced colorectal cancer

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Abstract

From our prospectively accrued database of patients with gastrointestinal cancer, 1057 patients with advanced colorectal cancer were identified with the aim of determining predictive factors for survival of greater than 2 years and to use this information to develop a predictive nomogram. Patient's baseline characteristics, type and number of chemotherapy regimens received, and response to chemotherapy were assessed by univariate and multivariate logistic regression comparing those who survived greater than or less than 2 years. A total of 161 (15.2%) patients survived more than 2 years, so-called long survivors (LS). In multivariate analysis, positive predictive factors for LS were: good performance status (PS), normal serum carcinoembryonic antigen (CEA), rectal primary, Dukes' stage A–B, well or moderate differentiation, two or less disease sites, response to chemotherapy and treatment used protracted venous infusion (PVI) 5-fluorouracil (5-FU) in first-line chemotherapy, and the increasing number of chemotherapy treatments received. From these PS, CEA, number of sites and response to first-line chemotherapy were used to develop a nomogram capable of predicting the probability of survival beyond 2 years for an individual patient. This large study confirmed the relevance of known prognostic factors in metastatic colorectal cancer and demonstrated the importance of response to chemotherapy as an independent factor to predict LS. By combining these, we developed a nomogram which provides information which is likely to prove useful in the management of patients with advanced colorectal cancer.

Keywords: Colorectal; Nomogram; Survival; Prognosis

1. Introduction

Colorectal cancer is the second most frequent malignancy and cause of death in males in the UK and the third most common in females. In the European Union and the USA it accounts for 165 000 deaths per annum [1]. Metastatic disease is generally considered incurable and treatment is largely aimed at palliation. Randomised trials of best supportive care versus chemotherapy have established the benefit of cytotoxic treatment in this setting in terms of survival, clinical benefit (improvement in performance status and disease-related symptoms), and quality of life [2–6]. First-line chemotherapy is now considered routine and there is now increasing evidence to support the use of second-line treatment [2].

Overall survival is, however, generally poor, with medians in randomised trials of chemotherapy-treated patients ranging from 9 to 15 months, and generally approximately 12 months [7,8]. Evidence from recent trials with combination therapy and new agents, such as irinotecan and oxaliplatin, appear to demonstrate that median survival of 15–17 months is possible [9,10]. Survival beyond 2 years remains unusual, however, and therefore for the purposes of this study we have considered those patients who survive for this period as long survivors (LS).

There are a number of recognised prognostic factors in metastatic colorectal cancer, including performance status (PS), tumour differentiation, serum carcinoembryonic antigen (CEA) levels, tumour size, primary tumour location and original Dukes' stage [11–13], but to our knowledge there is no method available to combine them in practice to predict LS following chemotherapy.

The aims of this study were to investigate the role prognostic factors might have in predicting long-term survival beyond 2 years, and to assess whether there was

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any interaction between the effect of treatment with these predictors. By studying a large group of patients we also aimed to determine the groups who receive benefit from second, third and even fourth-line chemotherapy. With this information, we developed a nomogram that may facilitate more informed decisions regarding the use of palliative chemotherapy, by both the patient and their families.

2. Patients and methods

2.1. Patient selection

Patients were identified for this study using a prospectively acquired database of patients referred to this hospital with gastrointestinal cancer. The population of relevance for this study were those diagnosed with advanced colorectal cancer between February 1990 and October 1998. Patients with less than 2 years follow-up were excluded from the analysis. All the patients had histologically proven adenocarcinoma of the colon or rectum which was locally advanced or metastatic. Locally advanced disease was defined as an inoperable primary tumour, partially resected primary or locally relapsed tumour without evidence of distant metastases. Patients may have had adjuvant chemotherapy or radiotherapy after surgery for their primary tumour, provided this was completed 6 months before relapse was diagnosed. Patients surviving over 2 years were defined as LS.

2.2. Chemotherapy

All patients received first-line chemotherapy, most of them (794 patients) enrolled in clinical trials, the details of which have been previously reported [2,9,14–20]. Some patients received two or more lines of chemotherapy, to a maximum of six lines of treatment.

The regimens used were:

1. Protracted venous infusion (PVI) 5-fluorouracil (5-FU) (300 mg/m^2/d via a portable pump and indwelling catheter), with or without interferon (IFN)-α (5-FU subcutaneously (s.c.) three times weekly), or with mitomycin C (MMC) (7 mg/m^2 intravenously (i.v.) every 6 weeks until a maximum of four courses), or in chronomodulated venous infusion (600–450 mg/m^2/day continuous infusion overnight between 10.45 pm and 9.45 am, with MMC), or associated with other drugs (cisplatin, carboplatin, carmustine).
2. Other 5-FU regimens (5-FU 425 mg/m^2 i.v. + leucovorin 20 mg/m^2 i.v. days 1–5 every 4 weeks; or 5-FU 400 mg/m^2 i.v. + leucovorin 200 mg/m^2 i.v. + 5-FU 400 mg/m^2 over 22 h, days 1–2 every 2 weeks, with or without interferon, or 5 days infusional 5-FU (750 mg/m^2/day for 5 days followed by weekly bolus 750 mg/m^2 i.v.) with or without IFN-α, or oral 5-FU (uracil/ftorafur 300 mg/m^2/day orally (p.o.) for 28 days every 35 days, or capecitabine 2500 mg/m^2/day p.o. 2 weeks treatment and 1 week rest).
3. Raltitrexed (3 mg/m^2 i.v. every 3 weeks).
4. Irinotecan (300–350 mg/m^2 i.v. every 3 weeks), or associated with raltitrexed.
5. Oxaliplatin and 5-FU (85–100 mg/m^2 i.v. day 1 + PVI 5-FU, every 2 weeks).
6. Other regimens such as MMC alone (7–10 mg/m^2 i.v. every 6 weeks), carmustine (200 mg/m^2 i.v. every 6 weeks) or investigational drugs.

2.3. Evaluation of response

Staging and measurement of disease was by computed tomography (CT) scan and, if appropriate, other radiological investigations or lower gastrointestinal (GI) endoscopy. Other recorded parameters included haematological and biochemical indices including serum CEA level pretreatment.

Patients' PS was graded according to the Eastern Cooperative Oncology Group (ECOG) scale and recorded at the initial consultation. Response to first and subsequent lines of therapy was classified using the World Health Organization (WHO) objective response criteria following serial CT scanning and repeating other staging investigations [21]. Toxicity was graded according to common toxicity criteria (CTC) [22] by physical examination, direct questioning and measurement of haematological and biochemical parameters.

2.4. Statistical methods

The aim of this study was to investigate the prognostic factors that predict for survival beyond 2 years in advanced colorectal cancer. Patients with follow-up less than 2 years were excluded from the analysis. Although this could introduce bias into the study if survival analysis methods were employed, the use of a binary endpoint, i.e. survival beyond 2 years versus death before 2 years justified this exclusion. The Chi-squared test was used to perform the univariate analysis, with Fisher's exact test used where appropriate. All patients in the study were included in the denominator for the calculation of response rate. Binary logistic regression analysis using the maximum likelihood model was used in this analysis to identify prognostic variables that predict for survival beyond 2 years. A P value of <0.05 was considered statistically significant.

Coefficients from the logistic regression analysis were converted into a 0–100 scale to remove the negativity for easy summation. The factor with the minimum

coefficient (i.e. CEA ⩾ 50 μg/l coefficient — 2.018) was converted to 100 points and CEA < 5 μg/l was converted to 0 points, all other coefficients conversions were relative to this (Fig. 1a). This allowed the coefficients to be easily summed and the total points evaluated. Total points from the coefficient conversion were then plotted against the probability of surviving to 2 years generated from the logistic regression model. The total points from the covariate pattern for a patient may be converted to the probability of surviving beyond 2 years (Fig. 1b). For example, a patient with the following covariate pattern: response to first-line treatment, with one metastatic site, CEA of 10 μg/l, PS 2, would have converted points 0, 0, 50, 73 respectively and total points 123. This can be converted on the conversion graph to a probability of surviving beyond 2 years of 14%.

3. Results

3.1. Patients' characteristics

There were 1399 patients treated in this period for advanced colorectal cancer although 342 patients had less than 2 years follow-up. Therefore, there were 1057 patients identified as suitable for analysis. The characteristics of the patients are listed in Table 1. Patients surviving more than 2 years numbered 161 (15.2%),

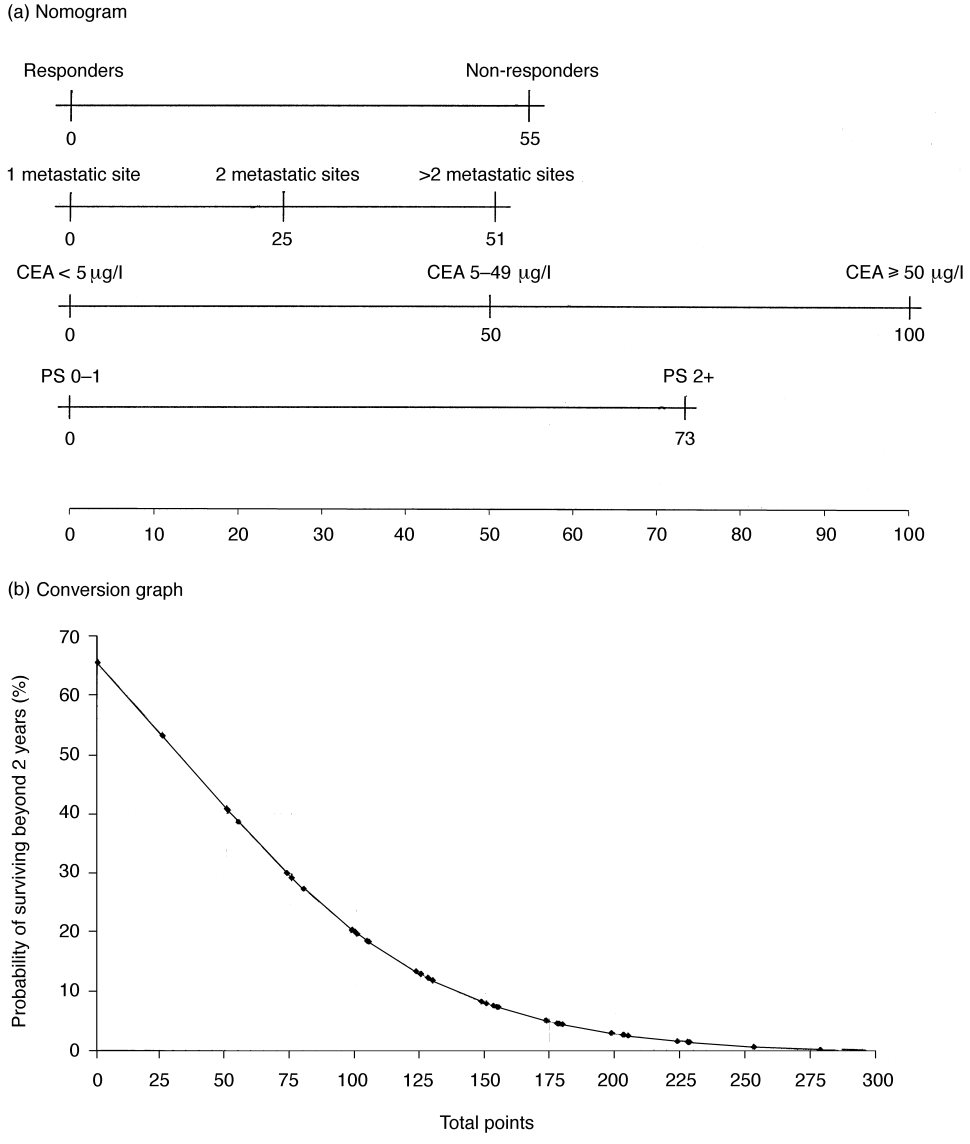

Fig. 1. Clinical algorithm based on 1057 patients with advanced colorectal cancer, treated at the Royal Marsden Hospital, Sutton, UK, for predicting the probability of surviving beyond 2 years. (a) Nomogram. (b) Conversion graph. Instruction for use: Identify patient's score for each factor listed in the nomogram. Each score is added to form a total. Locate this sum on 'total points' axis of conversion graph. The position at which the curve is crossed defines on the 'probability of surviving' axis the probability of surviving more than 2 years from the time of diagnosis of advanced disease. CEA, carcinoembryonic antigen; PS, performance status.

Table 1
Prognostic factors by patient characteristic

Characteristic	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)	*P* value
n of patients	1057 (100)	896 (84.8)	161 (15.2)	
Sex				
Male	629 (59.5)	542 (60.5)	87 (54.0)	0.120
Female	428 (40.5)	354 (39.5)	74 (46.0)	
Age (years)				
Median (range)	62 (16–85)	62 (16–85)	60 (27–78)	
Previous chemotherapy	140 (13.2)	113 (12.6)	27 (16.8)	
Previous radiotherapy	44 (4.2)	40 (4.5)	4 (2.5)	
PS				
0	239 (22.6)	190 (21.2)	49 (30.4)	
1	503 (47.6)	407 (45.4)	96 (59.6)	< 0.0001
2	245 (23.2)	230 (25.7)	15 (9.3)	
3–4	50 (4.7)	50 (5.6)	–	
Unknown	20 (1.9)	19 (2.1)	1 (0.6)	
Differentiation				
Well	34 (3.2)	33 (3.7)	1 (0.6)	
Moderate	796 (75.3)	659 (73.5)	137 (85.1)	0.010
Poor	150 (14.2)	137 (15.3)	13 (8.1)	
Unknown	77 (7.3)	67 (7.5)	10 (6.2)	
Primary tumour site				
Caecum/right colon	249 (23.6)	228 (25.4)	21 (13.0)	0.018
Transverse colon	70 (6.6)	58 (6.5)	12 (7.5)	
Left colon	72 (6.8)	65 (7.3)	7 (4.3)	
Sigmoid colon	267 (25.3)	226 (25.2)	41 (25.5)	
Rectum/rectosigmoid	392 (37.1)	313 (34.9)	79 (49.1)	< 0.0001
Synchronous colorectal primaries	7 (0.7)	6 (0.7)	1 (0.6)	
Original Dukes' stage				
A–B	202 (19.1)	153 (17.1)	49 (30.4)	0.0002
C	401 (37.9)	350 (39.1)	51 (31.7)	
D	427 (40.4)	371 (41.4)	56 (34.8)	
Unknown	27 (2.6)	22 (2.5)	5 (3.1)	
CEA (μg/l)				
< 5	220 (20.8)	142 (15.8)	78 (48.4)	< 0.0001
5–49	337 (31.9)	285 (31.8)	52 (32.3)	
⩾ 50	433 (41.0)	407 (38.5)	26 (16.1)	
Unknown	67 (6.3)	62 (58.7)	5 (3.1)	
Tumour site				
Liver	716 (67.7)	622 (69.4)	94 (58.4)	0.005
Lung	291 (27.5)	252 (28.1)	39 (24.2)	0.310
Locoregional	275 (26.0)	230 (25.7)	45 (28.0)	0.544
Nodal	233 (22.0)	215 (24.0)	18 (11.2)	0.0003
Peritoneum	178 (16.8)	159 (17.7)	19 (11.8)	0.064
Bone or bone marrow	38 (3.6)	37 (4.1)	1 (0.6)	
Other	177 (16.7)	164 (18.3)	13 (8.1)	
No. sites of disease				
1	512 (48.4)	408 (45.5)	104 (64.6)	
2	329 (31.1)	283 (31.6)	46 (28.6)	< 0.0001
3	147 (13.9)	136 (15.2)	11 (6.8)	
4	54 (5.1)	54 (6.0)	–	
5	9 (0.9)	9 (1.0)	–	
6	6 (0.6)	6 (0.7)	–	
Surgery for metastasis	34 (3.2)	17 (1.9)	17 (10.6)	< 0.0001
Radiotherapy in metastatic disease	199 (18.8)	147 (16.4)	52 (32.3)	
Curative intent	34 (3.2)	19 (2.1)	15 (9.3)	< 0.0001
Palliative intent	165 (15.6)	128 (14.3)	37 (23.0)	

PS, performance status; CEA, carcinoembryonic antigen.

Table 2
Outcome of treatment (%) in each chemotherapy line

Response	First-line			Second-line			Third-line			Fourth-line		
	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)
CR	30 (2.8)	12 (1.3)	18 (11.2)	1 (0.2)	–	1 (0.9)	–	–	–	–	–	–
PR	261 (24.7)	204 (22.8)	57 (35.4)	29 (6.7)	13 (4.0)	16 (14.5)	5 (2.9)	1 (0.9)	4 (6.7)	4 (7.0)	1 (3.8)	3 (9.7)
SD	448 (42.4)	374 (41.7)	74 (46.0)	186 (43.1)	130 (40.4)	56 (50.9)	85 (50.0)	54 (49.1)	31 (51.7)	23 (40.4)	10 (38.5)	13 (41.9)
PD	303 (28.7)	299 (33.4)	4 (2.5)	206 (47.7)	174 (54.0)	32 (29.1)	77 (45.3)	54 (49.1)	23 (38.3)	30 (52.6)	15 (57.7)	15 (48.4)
NE	15 (1.4)	7 (0.8)	8 (5.0)	10 (2.3)	5 (1.6)	5 (4.5)	3 (1.8)	1 (0.9)	2 (3.3)	–	–	–
Total	1057 (100)	896 (100)	161 (100)	432 (40.9)	322 (35.9)	110 (68.3)	170 (16.1)	110 (12.3)	60 (37.3)	57 (5.4)	26 (2.9)	31 (19.3)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

those less than 2 years 896 (84.8%). More patients were male (59.5%), the median age was 62 years (range 16–85). There were 89 (8.4%) patients with locally advanced disease, 968 (91.6%) with metastatic disease at one or more sites, with liver the most frequent site of involvement (67.7% of patients).

3.2. Response and toxicity

Of 1057 patients treated with first-line chemotherapy, objective responses were seen in 291 patients, including 30 (2.8%) complete responses (CR) and 261 (24.7%) partial responses (PR) (Table 2). 15 patients (1.4%) were considered unassessable for response, although they are included in the denominator of the reported response rate. First-line chemotherapy regimens included PVI 5-FU (single agent or in combination chemotherapy) in 706 (66.8%) patients, other 5-FU regimens in 210 (19.9%), and raltitrexed in 105 (9.9%) (Table 3). Hepatic deposits were most likely to respond to first-line chemotherapy, peritoneal metastases were least likely (Table 4).

432 patients who progressed during or following first-line treatment were offered second-line chemotherapy. The majority were again treated with PVI 5-FU (46.5%; $n=201$). Irinotecan therapy was administered to 11.3% ($n=49$) and 31.3 ($n=135$) received other agents. An overall response rate of 6.9% and disease stabilisation rate of 43.1% was observed. Of patients who received third- and fourth-line of chemotherapy treatment, objective responses were seen in 5 of 170 (2.9%) and 4 of 57 (7%) patients, respectively. Stable disease was observed in 85 (50.0%) and 23 (40.4%), respectively.

Grade 3 and 4 toxicities for each line of chemotherapy are summarised in Table 5. The most frequently observed toxicities were leucopenia and neutropenia, infection and diarrhoea. Apart from a trend to an increasing incidence of leucopenia and neutropenia, we observed a constant rate of toxic effects with the second and subsequent lines of chemotherapy. There were 5 treatment-related deaths, all of which occurred in patients receiving first-line chemotherapy (4 with the 5-day infusional 5-FU plus IFN-α regimen and 1 with the PVI

Table 3
Delivered regimens at patients (%) in each chemotherapy line

Treatments	First-line			Second-line			Third-line			Fourth-line		
	Overall *n* (%)	2 years *n* (%)	> 2 years *n* (%)	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)
PVI 5-FU	706 (66.8)	578 (64.5)	128 (79.5)	201 (46.5)	120 (37.3)	81 (73.6)	62 (36.5)	36 (32.7)	26 (43.3)	20 (35.1)	8 (30.8)	12 (38.7)
Other 5-FU	210 (19.9)	194 (21.7)	16 (9.9)	20 (4.6)	14 (4.3)	6 (5.5)	3 (1.8)	–	3 (5.0)	3 (5.3)	1 (3.8)	2 (6.5)
Raltitrexed	105 (9.9)	90 (10.0)	15 (9.3)	7 (1.6)	5 (1.6)	2 (1.8)	1 (0.6)	1 (0.9)	–	4 (7.0)	4 (15.4)	–
Irinotecan	10 (0.9)	9 (1.0)	1 (0.6)	49 (11.3)	44 (13.7)	5 (4.5)	31 (18.2)	16 (14.5)	15 (25.0)	9 (15.8)	1 (3.8)	8 (25.8)
5-FU/oxaliplatin	6 (0.6)	6 (0.7)	–	20 (4.6)	17 (5.3)	3 (2.7)	12 (7.1)	8 (7.3)	4 (6.7)	3 (5.3)	2 (7.7)	1 (3.2)
Other	20 (1.9)	19 (2.1)	1 (0.6)	135 (31.3)	122 (37.9)	13 (11.8)	61 (35.9)	49 (44.5)	12 (20.0)	18 (31.6)	10 (38.5)	8 (25.8)
Total	1057 (100)	896 (100)	161 (100)	432 (40.9)	322 (35.9)	110 (68.3)	170 (16.1)	110 (12.3)	60 (37.3)	57 (5.4)	26 (2.9)	31 (19.3)

PVI 5-FU, protracted venous infusion 5-fluorouracil with or without interferon-α, with or without mitomycin-C, or in chronomodulated venous infusion; other 5-FU, bolus 5-FU + leucovorin, or 48-h bolus and infusional bi-weekly 5-FU + leucovorin with or without interferon-α, or 5-day infusional 5-FU with or without interferon-α, or oral 5-FU; irinotecan, irinotecan with or without raltitrexed; other, mitomycin-C, carmustine or investigational drugs.

Table 4
Response (%) by major sites with first-line chemotherapy

Response	Overall *n* (%)	< 2 years *n* (%)	> 2 years *n* (%)	*P* value
Overall	291/1057 (27.5)	216/896 (24.1)	75/161 (46.6)	< 0.0001
Liver	212/716 (29.6)	159/622 (25.6)	53/94 (56.4)	< 0.0001
Nodes	63/233 (27.0)	53/215 (24.7)	10/18 (55.6)	0.014
Locoregional	65/275 (23.6)	50/230 (21.7)	15/45 (33.3)	0.094
Lung	64/291 (22.0)	46/252 (18.3)	18/39 (46.2)	0.0001
Peritoneal	35/178 (19.7)	29/159 (18.2)	6/19 (31.6)	0.948

Table 5
WHO grade 3–4 major toxicities in each chemotherapy line (all regimens) ($n = 1057$)

% With	Mucositis	Plantar-palmar	Nausea	Diarrhoea	Leucopenia	Neutropenia	Thrombocytopenia	Infection
First-line	4.2	5.9	3.8	9.4	4.6	8.4	2.9	9.8
Second-line	2.2	3.3	2.2	4.7	6.1	6.8	3.7	5.0
Third-line	2.2	2.9	5.8	8.0	7.1	11.0	5.9	7.3
Fourth-line	–	4.1	–	4.0	12.3	15.8	3.5	8.2

5-FU plus IFN-α). No significant differences in terms of toxicity rates were found in the two groups of patients.

3.3. Times to treatment failure

The median follow-up was 38 months (range: 24.5–87 months). The median time to treatment failure (TTF) with first- and second-line chemotherapy was 6.1 and 3.7 months, respectively (19.6 and 8.1 months in LS). The differences in median TTF between the two groups was reduced with third- and fourth-line chemotherapy, but was still longer in the LS group, as shown in Table 6.

3.4. Univariate predictors of long survival

Good PS (ECOG grade 0–1), at time of the first treatment for metastatic disease was a strong predictor of LS; well or moderate differentiation of the primary tumour was associated with a better outcome than those with poorly differentiated tumours (Table 1).

Primary disease located in the rectum or rectosigmoid junction was a good predictor of survival compared with disease located in the colon. Among patients with colon cancer, disease in the caecum and ascending colon cancer indicated a poorer prognosis compared with transverse or descending or sigmoid colon cancer ($P = 0.018$). Dukes' stages A–B at diagnosis was significantly associated with LS.

Table 6
Median time to failure (months) in each chemotherapy line

	First-line	Second-line	Third-line	Fourth-line
Overall	6.1	3.7	2.8	2.8
< 2 years	5.4	3.2	2.5	2.3
> 2 years	19.6	8.1	5.1	3.5

Serum CEA levels were measured prior to treatment in 93.7% patients. An elevated CEA was significantly correlated with poor survival at both the lower cut-off of 5 μg/l and at a higher cut-off value of 50 μg/l. Other factors that had prognostic significance as predictors for LS were location of metastases to liver or distant nodes, and spread to no more than two metastatic sites.

LS patients were significantly more likely to have undergone surgical resection of local recurrence or resectable metastases, or to have received radical dose external beam radiotherapy for locally advanced or unresectable tumours (Table 1). Thirty-four surgical resections were performed, and most of them were for abdominal-pelvic recurrences (13 patients, of whom 8 patients were in the LS group). The remainder were for liver and lung metastases (13 and 4 patients, respectively, of whom 5 and 3 patients were among the LS). Postoperative chemotherapy was generally administered to those patients who underwent surgery. External beam radiotherapy with a curative intent was administered to 34 patients. This was preoperative (concomitant or sequential to a chemotherapy treatment) for locally advanced or unresectable rectosigmoid in 29 patients, of which 15 were LS. 5 patients had radiotherapy to other colonic primary site tumours.

LS had a higher overall response rate to first-line chemotherapy (46.6 versus 24.1%, respectively, $P < 0.0001$), and this difference was also observed in CR rate (11.2% versus 1.3%, $P < 0.0001$) (Table 2). The higher response rate of liver, lung and nodal metastases significantly predicted a better outcome, as shown in Table 4. Moreover, LS were significantly more likely to have received PVI 5-FU and less likely to have had bolus 5-FU therapy compared with short-survivors (79.5 and 9.9% versus 64.5 and 21.7%, respectively, $P < 0.0001$) (Table 3).

Among 432 patients that received second-line chemotherapy, a significantly higher number were in the LS group (68.3 versus 35.9%, $P < 0.0001$), with again a superior overall response rate (15.5 versus 4.0%, $P < 0.0001$) (Table 2). LS received significantly more PVI 5-FU-based second-line chemotherapy compared with short-survivors that were treated especially with 'other' regimens ($P < 0.0001$) (Table 3).

Among patients receiving third- and fourth-line chemotherapy a higher response rate was observed in LS (Table 2), and the LS were treated mainly with PVI 5-FU and irinotecan chemotherapy compared with patients surviving less than 2 years who had received more alternate 'other' regimens (Table 3).

Sex, age and previous treatments received were not significant at univariate analysis.

3.5. Multivariate analysis

A multivariate logistic regression model was used to assess the simultaneous effects of various factors on predicting a survival longer than 2 years. Factors that retained significance included a good performance status, well or moderately differentiated tumour, primary disease in the rectum, Dukes' stages A–B at diagnosis, serum CEA levels < 5 μg/l, two or less sites of disease, overall response rate and treatment used (PVI 5-FU) in first-line chemotherapy, and the increasing number of chemotherapy regimens received (Table 7).

3.6. Nomogram

A nomogram was constructed based on the most accessible prognostic factors from the multivariate analysis, including baseline predictors such as PS, serum CEA levels, and number of disease sites, combined with the response to the first-line chemotherapy (Fig. 1a).

The nomogram gives a score which is converted to a probability of surviving longer than 2 years from the time of diagnosis of advanced disease, using the conversion graph (Fig. 1b). A patient who scores 0 will have the best prognosis. However, it is also seen that, for example, a patient with a CEA $\geqslant 50$ μg/l who responded and with two metastatic sites will have a lower probability of surviving more than 2 years compared with a patient who did not respond, but has only one metastatic site and normal CEA and PS.

4. Discussion

The major aim of this study was to determine whether prognostic clinical parameters formulated together as a nomogram are capable of predicting for survival longer than 2 years. Our cohort appears to be representative of the wider population of patients with advanced colorectal cancer with a similar 2-year survival rate to other previously reported series [23], despite approximately 25% of patients in our series being treated outside the context of a clinical trial. In developing a predictive model we were able to confirm a number of previously reported prognostic factors. As observed in a meta-analysis [8] good performance status (ECOG grade 0–1) was one of the most reliable factors found to predict for survival beyond 2 years in metastatic disease (Table 7). In addition, we confirmed the following as predictors of survival over 2 years, using multivariate analysis: well or moderate differentiation of the tumour; low number of metastatic disease sites ($\leqslant 2$) [11,13]; low (< 5 μg/l) serum CEA levels [24]; primary site of the tumour in the rectum [8,23].

The resection of liver or lung metastases from colorectal cancer has resulted in long-term survival [25], and recurrence is delayed and possibly prevented by the use of postoperative chemotherapy [26]. In addition, preliminary phase I–II trials have shown, in patients with a locally advanced rectal cancer, that preoperative chemoradiotherapy treatment has yielded, not only better local control rates, but also improved survival rates as a result of tumour downstaging [27,28]. These data are consistent with the results of our univariate analysis where surgical resections of locoregional relapses or

Table 7
Independent predictor factors for survival longer than 2 years

Predictor	*P* value	Odds ratio (95% confidence interval)
PS ($\geqslant 2$)	0.002	0.34 (0.17–0.66)
Differentiation (poor)	0.004	0.36 (0.18–0.73)
Primary site (colon versus rectum)	0.021	0.60 (0.39–0.93)
Dukes' stage (increasing)	0.009	0.69 (0.52–0.91)
No. sites disease (increasing)	< 0.0001	0.62 (0.48–0.81)
CEA ($\geqslant 5$ μg/l)	< 0.0001	0.15 (0.10–0.24)
Response rate	< 0.0001	2.57 (1.65–3.99)
Treatment (other 5-FU versus PVI 5-FU)	0.029	0.45 (0.22–0.92)
(Raltitrexed/other versus PVI 5-FU)	0.201	0.66 (0.35–1.25)
No. chemotherapy lines (increasing)	< 0.0001	1.97 (1.59–2.45)

PS, performance status; CEA, carcinoembryonic antigen; PVI, protracted venous infusion.

resectable metastases, and intentional curative neoadjuvant combined treatment for unresectable and locally advanced tumours was found to significantly predict for LS (Table 1). Unfortunately, as there were only a small number of patients treated in this fashion, the two factors could not be included in the multivariate analysis to assess their role as independent predictors.

A recent meta-analysis concluded that continuous infusion of 5-FU is superior to bolus administration of 5-FU in terms of survival in advanced colorectal cancer [8]. Our multivariate analysis confirmed that PVI 5-FU in first-line chemotherapy is also a strong independent factor of a survival longer than 2 years if compared with other 5-FU regimens (Table 7). No differences were detected comparing PVI 5-FU and raltitrexed in this setting. The response to first-line chemotherapy, in terms of complete and overall responses, was also seen to be a major independent predictor in our analysis. The importance of response and treatment received was again seen in second-line chemotherapy, although it was not possible to confirm this by multivariate analysis given the low numbers. Overall, however, these results do lend support to the use of infusional 5-FU over bolus delivery.

Our data support response to chemotherapy as being a predictor of LS. This has previously been reported in an analysis of prognostic factors in colorectal cancer with liver metastases alone [13] Kemeny and colleagues [12] documented the partial tumour response to intrahepatic chemotherapy as a statistically significant prognostic factor in patients with hepatic metastases from colorectal cancer (18.7 months versus 11.7 months). Our findings underlined the central role of objective response to predict a LS, but in a larger group of patients with diffuse metastatic disease and treated with systemic chemotherapy.

The small number of patients treated with a third- or fourth-line chemotherapy did not allow a meaningful statistical analysis, but we did observe that LS were more likely to have received PVI 5-FU-based or irinotecan chemotherapy rather than alternative cytotoxic drugs (Table 3). Chemotherapy regimens such as MMC alone, carmustine or other investigational drugs, were not associated with objective responses, and since these represented approximately 30% of all treatments administered as second-, third- and fourth-line, the response rate is likely to have been influenced by this (Tables 2 and 3). However, even if the overall response rate was not high, the median time to failure (TTF) of 3.7 months observed in second-line chemotherapy is comparable with that of other recent trials [2,29], with a remarkable median TTF of 8.1 months in the long-survivors group (Table 6). Furthermore, with third- and fourth-line chemotherapy, in spite of the poor response rate, we observed an high overall rate of disease stabilisation (Table 2) with a meaningful median overall TTF of those patients with stable disease of 5.4 and 4.5 months, respectively. Although not designed to investigate the role of third- and fourth-line chemotherapy, the data do appear to argue for a role for further chemotherapy in selected patients.

The number of lines of chemotherapy regimens received was also an independent predictor in multivariate analysis, although obviously this may purely be a reflection of long survival itself.

Toxicities observed with chemotherapy did not substantially differ in terms of type and incidence from those described in previous reports with the same setting of patients. Furthermore, patients who received second-, third-, or fourth-line chemotherapy did not experience an increasing rate of toxic effects, apart from an increasing incidence of leucopenia and neutropenia reflecting the increased use of non-5-FU drugs with different toxicity profiles. All 5 toxic deaths occurred with first-line chemotherapy. Although we show only the cumulative rate of toxic effects, all regimens administered were well tolerated in each line of chemotherapy.

From the prognostic factors assessed at multivariate analysis we developed a nomogram using those factors we felt would be available following first-line therapy. Obviously, CEA, PS and number of metastatic sites are easily assessable. Given that chemotherapy regimens used may vary, we elected not to use this determinant. We did, however, consider that by using the response to first-line chemotherapy this would allow for an assessment at completion of the initial treatment. Thus, we have designed the nomogram to assess outlook following completion of first-line therapy using baseline factors and tumour response. It is postulated that this may be useful in discussion with patients as to prognosis and the relative benefit of further lines of chemotherapy.

Other factors could have been included in this nomogram, i.e. Dukes' stage, primary site, tumour differentiation. However, when other prognostic factors were added, the probability of surviving more than 2 years did not exceed 66%. Thus, keeping the tool as simple as possible, they were not included.

Using the nomogram one can see, not surprisingly, that patients whose total score is 0 will have the best prognosis and the highest probability of surviving more than 2 years. However, there remains a heterogeneous group for which the outlook is less obvious. If anything this nomogram illustrates the wide range of outcomes and that although response is a major independent predictor, one should also consider a number of other factors. The example given should serve to show that non-responders with good prognostic factors can be considered on an equal par with responders in certain situations and may also be candidates for further lines of chemotherapy. Historically, response rates in colorectal cancer are relatively low. However, new non-cross-resistant agents and combinations, such as irinotecan and oxaliplatin, have recently shown higher activity

both in first- and second-line chemotherapy, with a significant impact on survival and quality of life [29–31]. It would thus be expected that in appropriately selected patients these new active drugs give valuable therapeutic options and may also improve the number of LS. This nomogram may form the basis of a method of selecting those patients best served by additional chemotherapy.

In conclusion, we have confirmed the relevance of known prognostic factors in metastatic colorectal cancer in a large population and shown the importance of response to chemotherapy as an independent factor to predict long survival. By combining these, we have developed a clinical nomogram that could assist in the management of these patients and we plan to evaluate its use further.

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