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Does a patient's self-reported health-related quality of life predict survival beyond key biomedical data in advanced colorectal cancer?

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ABSTRACT

The purpose of this study was to determine whether baseline patients' self reported health-related quality of life (HRQOL) parameters could predict survival beyond key biomedical prognostic factors in patients with metastatic colorectal cancer. The analysis was conducted on 299 patients. HRQOL baseline scores were assessed using the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core30 (EORTC QLQ-C30). The Cox proportional hazards regression model was used for both univariate and multivariate analyses of survival. In addition, a bootstrap resampling technique was used to assess the stability of the outcomes.

The final multivariate Cox regression model retained four variables as independent prognostic factors for survival: white blood cell (WBC) count with a hazard ratio (HR) of 1.961 (95% CI, 1.439–2.672; $P < 0.001$), alkaline phosphatase with HR = 1.509 (95% CI, 1.126–2.022; $P = 0.005$), number of sites involved with HR = 1.108 (95% CI, 1.024–1.198; $P = 0.01$) and the patient's score on the social functioning scale with HR = 0.991 (95% CI, 0.987–0.996; $P < 0.001$) which translates into a 9% decrease in the patient's hazard of death for any 10 point increase. The independent prognostic importance of social functioning and the stability of the final Cox regression model were also confirmed by the additional bootstrap model averaging analysis, based on 1000 bootstrap-generated samples. The results suggest that social functioning, acts as a prognostic measure of survival beyond a number of previously known biomedical parameters.

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1. Introduction

Colorectal cancer ranks second in terms of both incidence and mortality in more developed countries. Over 940,000 new colorectal cancer cases are diagnosed worldwide each year, which accounts for some 492,000 deaths [1]. Despite some advances made in the treatment of colorectal cancer, more than half of colorectal cancer patients die from metastatic disease [2].

Several studies have identified prognostic factors for survival in colorectal cancer. Recently, a large pivotal multivariate analysis of 3825 metastatic colorectal cancer patients, identified four key biomedical parameters: performance status, white blood cell (WBC) count, alkaline phosphatase and the number of involved metastatic sites [3]. The identification of independent prognostic factors could have important implications for routine clinical practice and research for many reasons, including a helpful guide in treatment decision making. In advanced-disease settings, this information could also assist clinicians to recalibrate clinical prediction of survival and optimize the use of palliative care [4]. From a clinical research perspective, the identification of prognostic factors for survival could better help stratify patients into randomized clinical trials and aid the interpretation of results in a more transparent way.

The general literature on this topic has traditionally investigated biomedical variables. However, a growing number of studies have also focused on investigating the prognostic value of patient self reported health-related quality of life (HRQOL) parameters. Over the last few years, methodologically robust studies have shown that HRQOL parameters predict length of survival beyond important traditional clinical variables. This evidence has been reproduced in various advanced cancer populations, including breast [5], lung [6], melanoma [7], prostate [8], and gastric cancer [9].

In light of this recent literature, the objective of this research was to evaluate if baseline HRQOL parameters could predict overall survival beyond a number of previously known key biomedical prognostic variables, in metastatic colorectal cancer patients. Very few studies have been conducted to investigate the value of HRQOL as a prognostic factor in colorectal cancer; available results are limited by small sample sizes or inadequate statistical control of known biomedical prognostic factors [10,11]. Furthermore, because of possible harmful multicollinearity, which may occur when including HRQOL variables for prognostic factor analysis, it might become difficult to disentangle its influence and thus obtain a reasonably precise estimate of the separate effects of the single predictor variables [12]. This is the first large international study investigating the prognostic value of HRQOL parameters in metastatic colorectal cancer, which also takes into account such problems as possible model selection instability.

2. Patients and methods

2.1. Study design

This work is based on data from a prospective multicenter randomized controlled trial (RCT) in advanced colorectal cancer patients, conducted by the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Group (EORTC Study 40952). Fifty-nine institutions participated, enrolling patients from seven countries. The primary endpoint of the trial was overall survival (OS), with HRQOL included as a secondary endpoint. In total, 497 patients with previously untreated metastatic colorectal cancer were randomly allocated into three arms: those receiving bolus fluorouracil (FU) 425 mg/m^2 intravenously + leucovorin (LV) 20 mg/m^2 on days 1–5 and repeated on day 28 (FU + LV), or FU 2600 mg/m^2 as 24-h infusion alone (FU_{24h}), or in combination with 500 mg/m^2 LV (FU_{24h} + LV) – all given weekly 6× followed by a 2-week rest period. After a median follow-up of more than three years, survival did not significantly differ between treatment groups (median FU + LV, 11.1 months; FU_{24h}, 13.0 months and FU_{24h} + LV, 13.7 months; $P = 0.72$). Full details of treatment schedule and treatment-related clinical outcomes have been previously reported [13].

2.2. Patients

To be eligible for inclusion in the trial, patients had to be diagnosed with adenocarcinoma of the colon or rectum, beyond a curative option by surgery. Patients were required to have a performance status of 2 or less, no previous chemotherapy for metastatic disease (with the exception of previous adjuvant treatment if it was completed at least 6 months before inclusion). Eligible patients were randomly assigned centrally after stratification for the following factors: institution, World Health Organization (WHO) performance status (0, 1 vs. 2), tumour assessability (measurable vs. nonmeasurable) and prior adjuvant pre-treatment (yes vs. no). The study, approved by the EORTC protocol review committee and the ethics committee of each participating center, was conducted in compliance with the Helsinki declaration. All patients provided written informed consent. Plausibility of the data was checked for all centers by the study coordinators.

2.3. HRQOL baseline assessment and variables examined

Baseline HRQOL was measured using the EORTC Quality of Life Questionnaire-Core 30 (version 2.0) (EORTC QLQ-C30), an internationally validated HRQOL questionnaire suitable for use with a generic cancer population. It is available in several languages and has proven robust psychometric properties [14]. Assessments were performed at baseline considering a time window of 15 days before or after randomization, but in any case before treatment start. To maximize compliance and minimize error variance, due to uncontrolled differences in the timing or other external aspects of the assessments, HRQOL data collection was an integral part of the clinical trial [15]. Wherever possible, the questionnaires were administered at the clinic, in a room where the patient would not be disturbed. EORTC guidelines for administering questionnaires were provided, ensuring a standard approach to the collection of HRQOL data. The EORTC QLQ-C30 scores were calculated using the recommended EORTC procedures [16]. These involved transformation of raw scores into a linear scale ranging from 0 to 100. In the case of missing items within a scale, the scale score was calculated using only those for

which values were available, provided at least half of the items in the scale were completed.

In order to reduce the risk due to multiple testing, we investigated the correlation matrix and excluded from the analysis, a priori, the HRQOL variables which were expected to have no prognostic value and had high intercorrelation with other EORTC QLQ-C30 scales. These excluded scales were: financial difficulties, insomnia, dyspnea, cognitive and role functioning. The analysis therefore investigated the following HRQOL parameters: physical, emotional and social functioning, fatigue, nausea/vomiting, pain, appetite loss, constipation, diarrhea and the global quality of life scale. The ten HRQOL variables described above were all included as continuous factors, using data from baseline assessments. Key biomedical prognostic parameters in colorectal cancer were included: performance status (continuous), WBC count (cut-off value $\geqslant 10 \times 10^9$/l), alkaline phosphatase (cut-off value $\geqslant$300 U/l), number of metastatic sites involved (continuous), presence of liver metastases (yes vs. no), previous adjuvant chemotherapy (yes vs. no) and primary site of disease (colon vs. rectum + rectosigmoid). For the WBC count and alkaline phosphatase the cut off values previously identified to independently predict survival in this population were used [3].

2.4. Statistical analysis

This exploratory analysis was conducted on 299 patients having baseline data, from the 90, 92 and 117 patients enrolled in FU_{24h}; FU_{24h} + LV and FU + LV arms, respectively. Overall survival (OS) was measured from the date of randomization to the date of death (due to any cause). Patients still alive at the time of analysis were censored at the last date known to be alive. Survival curves and probabilities were estimated using the Kaplan–Meier technique [17]. Differences between survival curves were assessed using the log-rank test [18]. The Cox proportional hazards regression model was used for both univariate and multivariate analyses of survival [19]. For the analysis of prognostic factors for survival, the proportionality assumption was checked for each of the variables under study by testing the dependency of their hazard ratio over time [20]. Pearson's correlation coefficients were used to investigate the association between different covariates. All analyses were stratified for treatment. When using a stepwise variable selection procedure to identify independent factors prognostic for survival, variables were added using forward selection according to a selection entry criterion of 0.05 and removed using backward elimination according to a selection stay criterion of 0.05. The importance of a prognostic factor was assessed via Wald-type test statistics, the hazard ratio and its 95% confidence interval for survival. A level of 5% of significance was used for both biomedical and HRQOL variables. The replication stability of the final model predicting OS was also investigated, using a bootstrap re-sampling procedure as proposed by Sauerbrei and colleagues [21], applied in the context of HRQOL by Van Steen and colleagues [12]. This technique generates a number of samples (each the same size as the original data set), by randomly selecting patients and replacing them before selecting the next patient (i.e., bootstrap resampling). The frequency of inclusion of the component variables in the Cox PH regression models, including all the selected covariates and stratified for treatment, fitted to each of these data sets using automatic forward stepwise selection (entry level of $\alpha = 0.05$), can be considered to be indicative for the importance of the factors [21]. However, when we are interested in the "best set" of prognostic factors (which we usually are) rather than in the "best independent" prognostic factor, we need to account for the correlation structure of the potential prognostic factors under consideration. Therefore, we calculated the model selection probabilities based on how many times a permissible model was selected in the bootstrap samples. These probabilities were then used as weights to obtain weighted averaged parameters [22]. All data analyses were performed using SAS version 8.02.

3. Results

Characteristics of all patients enrolled in the original trial were classified according to the availability of HRQOL data (Table 1). Overall, patient characteristics with or without baseline scores were well balanced, only the proportion of patients with liver metastasis was significantly higher in the group of patients without HRQOL data. There was no significant difference in median survival between patients with and without baseline HRQOL data, stratified for institution. All the following analyses are based on 299 patients having valid HRQOL baseline data. With 253 observed deaths and a reported overall median survival time of 14.23 months (95% CI = 12.09–16.23), the data were sufficiently mature to detect survival differences with a hazard ratio (HR) 0.7 (or smaller) with a power of 80% (given a two-sided test at the 5% significance level).

3.1. Univariate analysis of survival

The following HRQOL parameters: physical and social functioning, fatigue, nausea and vomiting, appetite loss and global quality of life were all found to predict length of survival. Also, important biomedical parameters predicted survival: performance status, number of sites involved, WBC count and alkaline phosphatase. Details are reported in Table 2.

3.2. Multivariate analysis of survival

The starting Cox multivariate model contained seven key biomedical variables and ten HRQOL parameters (Table 3). The final multivariate model retained three biomedical parameters: WBC count ($P < 0.001$), alkaline phosphatase ($P = 0.005$) and number of sites involved ($P = 0.01$). In addition, social functioning ($P < 0.001$) was also an independent prognostic factor for survival. Performance status and all the HRQOL scales that were significant in the univariate analyses were not retained in the final model at a 5% level (Table 4).

3.3. Bootstrap model averaging (MA)

In order to have greater insight into the stability of the final Cox model and evaluate the importance of a single variable being included as an independent factor in the model, we applied a bootstrap model averaging technique to the survival part of our data set based on 1000 bootstrap samples. We

Table 1 – Patient characteristics: difference between patients with and without HRQOL baseline assessment

Variables	HRQOL assessment available, N (%)		
	No (198)	Yes (299)	Total (no = 497)
Age			
Median	60.9	61.7	61.2
Range	23.6–75.8	29.4–76.1	23.6–76.1
Sex			
Male	115 (58.1)	180 (60.2)	295 (59.4)
Female	78 (39.4)	118 (39.5)	196 (39.4)
Missing	5 (2.5)	1 (0.3)	6 (1.2)
Weight loss			
None	110 (55.6)	151 (50.5)	261 (52.5)
Less 5%	43 (21.7)	77 (25.8)	120 (24.1)
6–10%	24 (12.1)	45 (15.1)	69 (13.9)
More 10%	13 (6.6)	20 (6.7)	33 (6.6)
Unknown	2 (1.0)	4 (1.3)	6 (1.2)
Missing	6 (3.0)	2 (0.7)	8 (1.6)
Performance status			
WHO 0	104 (52.5)	157 (52.5)	261 (52.5)
WHO 1	75 (37.9)	121 (40.5)	196 (39.4)
WHO 2	14 (7.1)	19 (6.4)	33 (6.6)
Missing	5 (2.5)	2 (0.7)	7 (1.4)
Adjuvant chemotherapy			
Yes	159 (80.3)	258 (86.3)	417 (83.9)
No	33 (16.7)	40 (13.4)	73 (14.7)
Missing	6 (3.0)	1 (0.3)	7 (1.4)
Liver metastases			
Yes	65 (32.8)	53 (17.7)	118 (23.7)
No	133 (67.2)	246 (82.3)	379 (76.3)
Site of primary tumour			
Colon	112 (56.6)	148 (49.5)	260 (52.3)
Rectum + rectosigmoid	81 (40.9)	150 (50.2)	231 (46.5)
Missing	5 (2.5)	1 (0.3)	6 (1.2)
Number of sites involved			
1	67 (33.8)	80 (26.8)	147 (29.6)
>1	131 (66.2)	219 (73.2)	350 (70.4)
White Blood Cell (WBC) count			
$\leqslant 10 \times 10^9$/l	160 (80.8)	231 (77.3)	391 (78.7)
$>10 \times 10^9$/l	38 (19.2)	68 (22.7)	106 (21.3)
Alkaline phosphatase (AP)			
⩽300 U/l	150 (75.8)	210 (70.2)	360 (72.4)
>300 U/l	48 (24.2)	89 (29.8)	137 (27.6)

included the variables shown to be prognostic in the univariate analysis with at least a $P < 0.1$. Fatigue was not included because of the high correlations with many of the other HRQOL variables. The results of the inclusion frequencies are listed in Table 5. This table lists the weighted averaged parameters (using model selection probabilities as weights), as well as estimates obtained from the most likely model and the full model containing all variables. The four highest inclusion frequencies were WBC count (94%), number of sites involved (74%), social functioning (73%) and alkaline phosphatase (63%) as being indicative for relevant prognostic factor candidates. We emphasize that the recorded inclusion frequencies highlight the importance of a single variable being included as an independent factor in the model. However, model selection probabilities do provide information about the joint occurrence of variables. Inspection of Table 6, listing the top 10 selected models out of 1000 generated, reveals that the most selected model is the one containing WBC count, alkaline phosphatase, number of sites involved and social functioning confirming this model as the most adequate. Interestingly, social functioning was selected in all the top 10 models whilst alkaline phosphatase, performance status and number of sites involved were not.

4. Discussion

Social functioning, as measured in this study by the EORTC QLQ-C30, is evaluated by a scale consisting of the following two items: 'Has your physical condition or medical treatment interfered with your family life?' and 'Has your physical con-

Table 2 – Univariate Cox regression analyses of survival

Variables	Hazard ratio (HR)	95% Confidence interval (CI)	P-value
Biomedical parameters			
Performance status	1.528	1.234–1.892	<0.001
Number of sites involved	1.119	1.038–1.207	0.003
WBC count	2.064	1.535–2.776	<0.001
Alkaline phosphatase	1.762	1.340–2.316	<0.001
Liver metastases	1.282	0.919–1.790	0.143
Adjuvant chemotherapy	0.909	0.631–1.310	0.609
Site of primary tumour	0.862	0.671–1.107	0.243
HRQOL parameters			
Global health status/QoL	0.990	0.984–0.996	0.001
Physical functioning	0.991	0.985–0.996	0.001
Emotional functioning	0.995	0.990–1.000	0.064
Social functioning	0.993	0.989–0.997	0.001
Fatigue	1.008	1.003–1.012	<0.001
Nausea/vomiting	1.010	1.002–1.017	0.009
Pain	1.003	0.999–1.007	0.117
Appetite loss	1.006	1.002–1.010	0.006
Constipation	1.004	0.999–1.009	0.101
Diarrhoea	1.005	1.000–1.009	0.054

WBC, white blood cell; QoL, quality of life.

Table 3 – Starting multivariate Cox regression model of survival

Variables	Hazard ratio (HR)	95% Confidence interval (CI)	P-value
Biomedical parameters			
Performance status	1.217	0.941–1.574	0.133
Number of sites involved	1.122	1.032–1.220	0.007
WBC count	1.989	1.415–2.794	<0.001
Alkaline phosphatase	1.404	1.006–1.958	0.046
Liver metastases	1.131	0.763–1.677	0.540
Adjuvant chemotherapy	1.478	0.980–2.231	0.062
Site of primary tumour	0.779	0.594–1.021	0.070
HRQOL parameters			
Global health status/QoL	0.995	0.987–1.004	0.266
Physical functioning	0.999	0.991–1.007	0.811
Emotional functioning	1.003	0.995–1.011	0.446
Social functioning	0.990	0.983–0.996	0.002
Fatigue	1.004	0.996–1.013	0.318
Nausea/vomiting	1.009	0.998–1.020	0.121
Pain	0.994	0.987–1.000	0.055
Appetite loss	0.997	0.991–1.003	0.325
Constipation	1.001	0.995–1.007	0.793
Diarrhoea	1.004	0.999–1.009	0.124

WBC, white blood cell; QoL, quality of life.

dition or medical treatment interfered with your social activities?'. This scale ranges from 0 to 100, with higher values representing better level of functioning. The main finding of this research is that patients' reported score on this scale provides independent prognostic information for survival beyond a number of previously known key prognostic biomedical parameters.

Table 4 – Final Cox multivariate regression model of survival

Variables	Hazard ratio (HR)	95% Confidence interval (CI)	P-value
WBC count	1.961	1.439–2.672	<0.001
Alkaline phosphatase	1.509	1.126–2.022	0.005
Number of sites involved	1.108	1.024–1.198	0.010
Social functioning	0.991	0.987–0.996	<0.001

WBC, white blood cell.

One possible limitation of the study is the HRQOL compliance at baseline was sub-optimal. However, patients who provided baseline HRQOL data were representative of the overall trial population in terms of survival outcomes. The available large patient sample ($N = 299$) consisted of a homogeneous population of metastatic patients from a prospective multicenter randomized trial with sufficient follow-up and mature survival data allowing for an adequately powered analysis. Data collection in this sample was of high quality with HRQOL measured by a psychometric robust questionnaire and biomedical parameters available for all patients. Furthermore, a recently developed state of the art statistical approach has been used to strengthen the classical Cox analysis which is usually used in prognostic factor studies. Firstly, we applied a bootstrap resampling procedure to investigate model selection instability [21,23]. Secondly, we used the information derived thereof for model averaging purposes [22].

Köhne and colleagues [3] recently conducted a pivotal study on 3825 metastatic colorectal cancer patients, analysing overall 23 potential predictor variables. The resulting final multivariate model of survival, also validated on a large independent dataset, retained four baseline variables: performance status, WBC count, alkaline phosphatase, and number of sites involved. The population of our study is not different from the one reported by Köhne and colleagues as both studies included metastatic colorectal cancer patients treated with 5-FU based chemotherapy. Given our research question, we consider the pivotal multivariate analysis conducted by Köhne and colleagues [3] as the benchmark evidence against which to test the prognostic value of HRQOL parameters. However, we also considered other possible relevant biomedical prognostic variables, identified in other studies with colorectal cancer patients: previous adjuvant chemotherapy, site of primary tumour, and liver involvement [24–26]. Our final Cox regression model retained WBC count, alkaline phosphatase, number of sites involved and social functioning. The additional investigation of the model stability, based on a bootstrap model-averaging technique [12], confirmed this model as the best prognostic model for survival (Table 6).

In our study, social functioning, as reported by patients themselves, was an independent prognostic factor and a 10 point increase for a patient's score on this scale at baseline,

Table 5 – Classical Cox estimates vs. model averaging (MA) estimates

Variables	Classical estimate HR (*P*-value)	Top model HR (*P*-value)	MA estimate HR (*P*-value)	Inclusion variable (%)
Biomedical parameters				
Performance status	1.528 (<0.001)	–	1.121 (<0.001)	43
Number of sites involved	1.119 (0.003)	1.108 (0.010)	1.090 (<0.001)	74
WBC count	2.064 (<0.001)	1.961 (<0.001)	1.840 (<0.001)	94
Alkaline phosphatase	1.762 (<0.001)	1.509 (0.005)	1.309 (<0.001)	63
Liver metastases	1.282 (0.143)	–	–	–
Adjuvant chemotherapy	0.909 (0.609)	–	–	–
Site of primary tumour	0.862 (0.243)	–	–	–
HRQOL parameters				
Global health status/QoL	0.990 (0.001)	–	0.998 (<0.001)	21
Physical functioning	0.991 (0.001)	–	0.999 (<0.001)	15
Emotional functioning	0.995 (0.064)	–	0.999 (0.932)	7
Social functioning	0.993 (0.001)	0.991 (<0.001)	0.993 (<0.001)	73
Fatigue	1.008 (<0.001)	–	–	–
Nausea/vomiting	1.010 (0.009)	–	1.001 (0.007)	23
Pain	1.003 (0.117)	–	–	–
Appetite loss	1.006 (0.006)	–	1.000 (0.581)	11
Constipation	1.004 (0.101)	–	–	–
Diarrhoea	1.005 (0.054)	–	1.001 (<0.001)	31

WBC, white blood cell; QoL, quality of life.

Table 6 – Top 10 selected models

Model No.	WBC	AP	WHO	No. of sites	QL	PF	EF	SF	NV	APL	DI	Count	%
1	1	1	0	1	0	0	0	1	0	0	0	55	5.5
2	1	1	0	0	0	0	0	1	0	0	0	37	3.7
3	1	1	0	1	0	0	0	1	0	0	1	36	3.6
4	1	0	0	1	0	0	0	1	0	0	0	35	3.5
5	1	1	1	0	0	0	0	1	0	0	0	31	3.1
6	1	1	1	1	0	0	0	1	0	0	0	29	2.9
7	1	1	0	1	0	0	0	1	1	0	0	27	2.7
8	1	0	1	1	0	0	0	1	0	0	1	26	2.6
9	1	0	0	1	0	0	0	1	1	0	0	25	2.5
10	1	0	1	1	0	0	0	1	0	0	0	22	2.2

Note. "Count" refers to the number of times the model was selected.
WBC, white blood cell; AP, alkaline phosphatase; QL, global quality of life; PF, physical functioning, EF, emotional functioning; SF, social functioning; NV, nausea and vomiting; APL, appetite loss; DI, diarrhoea; WHO, World Health Organization (performance status).

translates into a 9% decrease in the patient's hazard of death (Table 4). The prognostic importance of this HRQOL parameter was also confirmed by the additional analysis. Out of the 1000 bootstrap models-generated, social functioning was selected 73% (Table 5).

Our study supports previous evidence of the prognostic value of HRQOL data in colorectal cancer. Maisey and colleagues [11] also using the EORTC QLQ-C30 showed that baseline overall quality of life scale independently predicted survival and was also a more superior prognostic indicator than performance status. Although this study gave insight into this issue, a clear comparison with our results is not possible as they used a different set of biomedical parameters and did not investigate model selection instability. Also, Earlam and colleagues [10] compared the ability of the extent of liver disease on a computed tomography scan with HRQOL measured at the time of liver metastasis diagnosis to predict survival in 50 patients with colorectal liver metastasis. They demonstrated that HRQOL provides a better survival estimate than the measurement of tumour size. Nevertheless, as a different set of biomedical parameters was analyzed (not including WBC count) and different HRQOL measures were used, their results cannot be compared with present findings.

Our study also confirms previous evidence that patients' self-reported HRQOL parameters are independent prognostic factors for survival, even out performing performance status [27–29]. When compared with a basic physician-reported outcome such as performance status, social functioning seems to be more sensitive in picking up a patient's health condition. Whilst general cancer patients' HRQOL can be impaired in various areas, colorectal cancer patients may specifically suffer long-lasting pain and a reduction in functional and social well-being [30]. A recent large population-based study, using the EORTC QLQ-C30 to compare long-term HRQOL

issues between colorectal cancer patients and the general population, also showed that social functioning was the most impaired functioning scale [31]. This data could lend support to the sensitivity of the social functioning scale as measured by the EORTC QLQ-C30 in measuring important HRQOL aspects in colorectal cancer patients.

The mechanism underlying the association between HRQOL parameters and length of survival in cancer patients is not yet entirely clear. A possible explanation is that patients' HRQOL scores might reflect an early perception of the severity of the disease in a more accurate way than conventional prognostic indices. Thus, patients who report worse HRQOL scores are the ones with worse underlying disease [32]. Whilst further research is definitely needed to clarify this issue, at present, this explanation seems reasonable as it could also account for the contradictory findings of the prognostic value of HRQOL data in patients with or without distant metastasis [33]. If future studies were to confirm our findings, this could be used to facilitate clinical decision-making in a palliative care setting and could also have important implications for stratification of patients into risk groups for future clinical trials with metastatic colorectal cancer patients.

Conflict of interest statement

None declared.

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