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Baseline quality of life predicts survival in patients with advanced colorectal cancer

N.R. Maisey[a], A. Norman[a], M. Watson[b], M.J. Allen[a], M.E. Hill[a], D. Cunningham[a,*]

[a]*Department of Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK*
[b]*Psychological Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK*

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Abstract

The aim of this study was to investigate the influence of baseline quality of life (QoL) on survival in patients with advanced colorectal cancer. From 1992 to 1998, four randomised clinical trials in advanced colorectal cancer were conducted at this institution. The European Organization for Research and Treatment of Cancer-Quality of Life Core 30 (EORTC-QLQ-C30) questionnaire was completed prior to the commencement of chemotherapy. Analyses were performed on median-dichotomised baseline Quality of Life (QoL) and clinical prognostic factors. Baseline QoL questionnaires were completed by 501 patients. One-year survival was 38.3 and 72.5% ($P<0.0001$) for patients with global QoL scores below and above the median (67), respectively. Other than cognitive functioning, fatigue, appetite, constipation, diarrhoea and financial domains, all QoL scales were significant independent predictors of survival ($P<0.035$). In the final model, the global QoL score remained highly significant as an independent predictor of survival ($P<0.0001$). Baseline QoL is a strong independent predictor of survival in patients with advanced colorectal cancer. Measurements should be routinely recorded in clinical trials to stratify cohorts and aid in trial comparison.

Keywords: Colorectal cancer; Quality of life; Prognosis; Clinical trials

1. Introduction

Previous perceived lack of scientific value and practical difficulties contributed to skepticism surrounding the use of quality of life (QoL) data in oncology trials. However, it is now clear that high completion rates of QoL questionnaires are possible [1–3] and that QoL is a useful endpoint when measuring the impact of therapeutic manoeuvres. Its use in patients with colorectal cancer is no exception. Chemotherapy has been found to improve the QoL of patients as well as to prolong survival [4,5]. QoL measurements are of particular value in cancers with poor prognosis, as well as in the comparison of chemotherapy regimens that are unlikely to produce large differences in survival [6–8].

In addition to quantifying the impact of treatments, there is evidence to suggest that QoL data may also have a prognostic role. Baseline QoL has been demonstrated to predict survival in a number of cancer types including breast cancer [9,10], lung cancer [11], melanoma [12] and in large cohorts of patients with varied malignancies [13,14]. A similar finding in patients with colorectal cancer would be of great value. Several poor prognostic factors in colorectal cancer have been identified, such as performance status, tumour burden, liver function and haematological parameters [15–19], but a simple prognostic model for these patients does not exist. Such a model may allow the stratification of trial patients, as well as the comparison of outcomes between studies.

The aim of this study was to examine the prognostic value of baseline QoL measurements in patients with locally advanced and metastatic colorectal cancer treated with systemic chemotherapy within the context of clinical trials.

* Corresponding author. Tel.: +44-20-8661-3156; fax: +44-20-8643-9414.
E-mail address: david.cunningham@icr.ac.uk (D. Cunningham).

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2. Patients and methods

2.1. Patients

Between 1992 and 1998, four randomised clinical trials in advanced colorectal cancer were conducted at this institution. Details of these clinical trials have been presented elsewhere, but results are summarised in Table 1. Briefly, the COLO1 study randomised patients between protracted venous infusion (PVI) 5-fluorouracil (5-FU) with or without interferon [20]. The COLO2 study compared raltitrexed (Tomudex) with 5-FU, administered according to the Mayo schedule [21]. Patients in the Chromatic study received either PVI 5-FU with mitomycin-C (MMC) or chronomodulated 5-FU with MMC [22]. Finally, patients entering the COMBAT study were randomised between PVI 5-FU with MMC and PVI 5-FU alone [23]. Two of the above studies were multicentric (COLO2 and Chromatic), but recruitment numbers from our centre only are shown in Table 1. Informed consent was obtained from all patients, and studies received local ethical approval. This retrospective study reviewed data that had been recorded prospectively on the Royal Marsden Hospital gastrointestinal unit research database.

Table 1
Details of clinical trials

Trial	Arm	*n* (study)	*n* (QoL)	% ORR (%CR)	1-Year OS (%)
COLO 1	PVI 5-FU	80	58	33 (5)	48
	PVI 5-FU + IFN	80	57	22 (0)	43
COLO 2	Tomudex	10	9	19 (3)	47
	5-FU	8	8	18 (3)	52
COMBAT	PVI 5-FU	100	83	38 (3)	57
	PVI 5-FU + MMC	100	81	54 (5)	51
Chromatic	PVI 5-FU	160	116	43 (12)	65
	Chrono 5-FU	160	89	32 (5)	70

n (study), number recruited in study; *n* (QoL), number completing QoL questionnaire; ORR, overall response rate; CR, complete response; OS, overall survival; PVI, protracted venous infusion; 5-FU, 5-fluorouracil; IFN, interferon; MMC, mitomycin-C; chrono, chronomodulated.

2.2. QoL data

QoL was assessed using the European Organization for Research and Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) Version 1, which has been validated elsewhere [24,25]. This QoL tool is a 30-item questionnaire incorporating five functioning domains (physical, role, cognitive, emotional and social), nine symptom domains (fatigue, nausea and vomiting, pain, dyspnoea, sleep disturbance, appetite, constipation, diarrhoea and perceived financial impact of the disease and treatment) and a global QoL scale. QoL domains are composed of 1–5 questions rated on 2-, 4- or 7-point scales. Scores are normalised using a standard procedure to lie between 0 and 100. A high functioning score and a low symptomatic score reflect a superior QoL. Data were prospectively recorded and analyses were performed on median-dichotomised baseline QoL groups and clinical prognostic factors. The cut-point was taken as the median dichotomised score unless that score was 0 or 100. In that case, the cut-point was taken as all scores above 0 or below 100, respectively. In all four trials, the EORTC-QLQ-C30 QoL questionnaire was completed prior to the commencement of chemotherapy.

2.3. Statistical analysis

Preliminary univariate and multivariate analyses were performed on the QoL data and recognised prognostic indicators, recorded as categorical data. These included sex, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) (PS 0,1 versus PS 2), the presence or absence of metastatic disease, tumour location (right- versus left-sided lesions), the presence or absence of weight loss, serum albumin (above or below 40 g/l), haemoglobin (above or below 110 g/l), white cell count (above or below 9.0×10^9 cells/l) and carcinoembryonic antigen (CEA) (above or below the median value). A baseline multivariate model was created using the above factors, and was stratified for the Chromatic study since margin-positive disease were included in this trial. QoL data were entered into a Cox Multivariate model to ascertain independent prognostic markers. Survival curves were calculated by the Kaplan–Meier method, and were compared by the log-rank test.

3. Results

3.1. Patient demographics

A total of 631 patients were recruited into the four studies from our centre. Of these, 501 patients completed the baseline QoL questionnaire (see Table 1). These form the cohort of the present study. Almost all patients (98%) received 5-FU-based chemotherapy, with only 2% receiving raltitrexed. The median age was 62 years (range 33–82), 63% of patients were male, 82% had metastatic disease and 98% of patients were of PS 0–2. The site of the primary was as follows: 28% in the right colon (up to and including the splenic flexure), 36% in the left colon (up to and including the rectosigmoid junction) and 34% in the rectum. Synchronous primaries were found in 2% of patients. The overall response rate was 39%, of whom 6% achieved a complete response (CR), and 23% of patients progressed on treatment. With a median follow-up of 2.84 years (range

0.057–7.86 years), the median overall survival was 14.7 months (range 0.36–61.7 months). At the time of analysis, 81% of patients had died.

3.2. QoL and survival

3.2.1. Univariate analysis

A univariate analysis was performed to detect which of the various QoL domains, if any, were predictive for overall survival. Remarkably, other than perceived financial impact, all domains, both functioning and symptomatic, were found to significantly predict survival (see Table 2).

3.2.1.1. Functioning domains. Functioning domains were scored on a scale from 0 to 100, where a higher score signified a superior QoL. For each domain, scores equal to or above the cut-point were associated with a statistically significant improved overall survival. Patients who had a physical functioning score equal to or above the cut-point of 80 had a median survival of more than double (19.7 months versus 9.8 months, $P<0.0001$). Similarly, large differences in overall survival were observed for role and social functioning scores equal to or above the cut-point (17.6 months versus 10.5 months and 16.2 months versus 9.3 months, respectively). Although still statistically significant, the difference in overall survival for emotional and cognitive functioning was not as dramatic (15.8 months versus 12.9 months and 15.4 months versus 12.9 months, respectively). It is conceivable that tumour burden *per se* is not the only influence on emotional and cognitive functioning and other factors such as individual personality and social support may temper patients' response to these aspects of the questionnaire. In contrast, physical functioning is more likely to be influenced by the extent of the malignancy.

3.2.1.2. Symptom domains. Symptom domains were scored on a scale of 0–100. Unlike the functioning domains, a lower symptom score reflects a superior QoL. A score equal to or below the cut-point in all symptom domains, other than perceived financial impact, was associated with a statistically significant superior overall survival. In contrast to the functioning domains, the majority of the median values were highly skewed, with six of the nine values being 0. This may well be a result of the limited number of possible scores within each domain. For five of the six domains with a median value of 0 (dyspnoea, appetite, constipation, diarrhoea and perceived financial impact), patients are only required to answer a single question rated on a scale of 1–4, thus giving potential scores 0, 33, 66 and 100. In effect, scores below and above a median score of 0 parallel those who are completely asymptomatic and those who suffer any degree of the symptom in question. It is therefore not surprising that there is a statistically significant survival advantage for scores below the median value in these cases. However, the degree of superiority in overall survival for asymptomatic patients remains impressive. For example, patients who had a nausea and vomiting score of 0 had a median overall survival more than twice that of patients with a score above 0 (16.6 months versus 7.5 months, $P<0.0001$). Similarly, those with no dyspnoea, no appetite disturbance and no bowel disturbance had a significant

Table 2
Results of the univariate analysis of individual QoL domains; note that the figures quoted are for values below and above the cut-points, respectively

QoL Domain	Median score	*n*	Median OS (months)	1-Year OS (%)	Logrank HR	HR CI (95%)	Logrank *P* value
Functioning domains							
Physical	80	210/254	9.8/19.7	39.4/71.5	1.82	1.47–2.12	<0.0001
Role	100	215/279	10.5/17.6	45.4/71.5	1.66	1.35–1.93	<0001
Emotional	83	232/255	12.9/15.8	52.8/61.0	1.3	1.06–1.5	0.0097
Cognitive	83	115/375	12.9/15.4	51.0/60.4	1.42	1.11–1.71	0.0021
Symptom domains							
Fatigue	33	336/157	17.0/9.1	66.6/39.1	0.51	0.41–0.61	<0.0001
Nausea and vomiting	0	386/109	16.6/7.5	65.6/28.4	0.41	0.3–0.51	<0.0001
Pain	17	319/175	17.7/9.7	66.3/40.6	0.5	0.4–0.59	<0.0001
Dyspnoea	0	353/145	16.2/10.6	62.7/44.6	0.61	0.48–0.73	<0.0001
Sleep disturbance	33	381/120	15.7/9.8	62.4/41.6	0.66	0.51–0.79	0.0002
Appetite	0	309/191	17.1/9.8	67.3/41.1	0.55	0.44–0.64	<0.0001
Constipation	0	351/145	15.3/13.3	58.7/54.4	0.8	0.64–0.94	0.0368
Diarrhoea	0	373/121	15.4/12.1	60.0/49.1	0.76	0.6–0.91	0.0159
Financial	0	358/138	15.1/13.6	57.9/55.7	0.83	0.67–0.98	0.0949
Global QoL	67	217/275	9.1/20.7	38.3/72.5	2.23	1.8–2.61	<0.00001

OS, overall survival; HR, hazard ratio; QoL, quality of life.

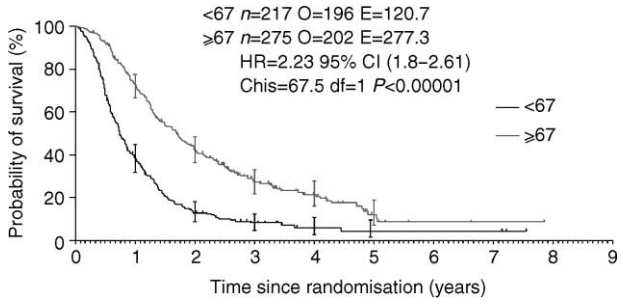

Fig. 1. Survival curve for baseline global QoL scores. O, observed; E, expected; HR, hazard ratio; CI, confidence interval; df. degrees of freedom.

superior overall survival. Symptoms of sleep disturbance, fatigue and pain also appeared to significantly predict survival in this univariate analysis.

The financial domain was not found to be a significant predictor of overall survival. Assessment was performed at baseline, prior to the start of chemotherapy. It is unlikely that any financial impact would be significant at such an early stage in the disease. In addition, many patients were elderly and past retirement age. Therefore income is less likely to be affected by intercurrent illness than for those in full-time employment.

3.2.1.3. Global QoL. To calculate the global QoL score, patients were required to answer two questions, each rated on a scale of 1–7. Thus, the final score has 14 possible outcomes on the 0–100 scale, rather than four possible outcomes as with many of the symptom scales. The median value for global QoL was 67, and the scores appeared to be well distributed with similar numbers of patients scoring below and above the median value (217 versus 275, respectively). Median overall survival in patients with scores equal to or above the cut-off was more than twice that of patients scoring below, and this result was highly statistically significant (20.7 months versus 9.1 months, $P<0.0001$). One-year overall survival was 72.5 and 38.3%, respectively, with a hazard ratio of 2.23 (95% confidence interval (CI): 1.8–2.6).

The survival curve for the median-dichotomised baseline global QoL score is shown in Fig. 1.

Table 3
Baseline multivariate model

Clinical variable	*P* value	Hazard ratio (95% CI)
Significant factor		
PS (0–1 versus 2)	<0.0001	1.71 (1.33–2.19)
Tumour location (left versus right)	0.033	0.79 (0.63–0.98)
Metastases (yes versus no)	0.04	1.38 (1.02–1.87)
Haemoglobin (⩽ or >110 g/l)	0.006	1.44 (1.11–1.87)
Weight loss (yes versus no)	0.003	1.39 (1.11–1.72)
CEA (⩾ versus < median value)	<0.0001	1.89 (1.47–2.42)
Albumin (⩽ versus >40 g/l)	<0.0001	0.62 (0.50–0.77)
Non-significant factors		
WCC (⩾ or $<9.0\times10^9$ cells/l)	0.47	–
Sex	0.77	–
Age	0.87	–

CI, confidence intervals; PS, performance status; CEA, carcinoembryonic antigen; WCC, white cell count.

3.2.2. Multivariate analysis

3.2.2.1. Baseline multivariate analysis. The baseline multivariate model was created using known prognostic factors without the QoL. Factors included in the baseline model were PS ($P<0.0001$), tumour location ($P=0.033$), the presence of metastatic disease ($P=0.04$), haemoglobin level ($P=0.006$), weight loss ($P=0.003$), CEA ($P<0.0001$) and albumin ($P<0.0001$) (see Table 3). Factors not included in the model that had failed to reach statistical significance were white cell count ($P=0.47$), sex ($P=0.77$) and age ($P=0.87$).

3.2.2.2. QoL as an independent prognostic factor for overall survival. Each QoL domain was tested against the baseline model shown in Table 3, with each domain being run separately. The majority of the QoL domains remained significant independent predictors of overall survival in the final multivariate model. These results are demonstrated in Table 4. Domains that were significant in the univariate analysis, but failed to reach

Table 4
The final multivariate model with QoL[a]

QoL domain	*P* value	Hazard ratio (95% CI)	Baseline factors excluded in the final model
Functioning domain			
Physical	0.01	1.35 (1.07–1.69)	[b]
Role	0.007	1.34 (1.08–1.66)	–
Social	0.003	1.43 (1.13–1.81)	[c]
Emotional	0.018	1.28 (1.04–1.57)	[b]
Cognitive	0.42	–	–
Symptom domains			
Fatigue	0.06	–	–
Nausea and vomiting	0.001	0.64 (0.49–0.84)	–
Pain	<0.0001	0.59 (0.48–0.74)	[d]
Dyspnoea	0.002	0.7 (0.56–0.88)	–
Sleep disturbance	0.001	0.67 (0.53–0.85)	–
Appetite	0.06	–	–
Constipation	0.68	–	–
Diarrhoea	0.08	–	–
Financial	0.36	–	–
Global QoL	<0.0001	2.17 (1.75–2.69)	[e]

[a] Each line is an individual multivariate model testing the relevant QoL domain against the baseline model shown in Table 4. Baseline factors that were no longer significant in the final model are shown in the right hand column.
[b] Tumour location.
[c] Presence of metastatic disease.
[d] Haemoglobin.
[e] Performance status.

significance in the multivariate model were cognitive functioning and symptoms of fatigue, appetite, constipation and diarrhoea. Perceived financial impact was not found to be a statistically significant predictor of survival in either the univariate or multivariate analysis.

Global QoL remained a highly significant independent predictor of overall survival in the final multivariate analysis. A score below the median cut-off for global QoL was an independent poor prognostic factor, with a hazard ratio of 2.17 (95% CIs 1.75–2.69, $P < 0.0001$).

3.2.2.3. Excluded baseline prognostic factors in the final model. Each QoL domain was tested separately against the baseline model. Because of interaction between prognostic factors and competing risks between them, factors that were significant independent predictors of survival in the baseline multivariate model in some cases failed to reach significance in the final model. This is illustrated in Table 4. PS was no longer significant in the final model that included global QoL.

4. Discussion

We have found that baseline QoL measurements are significant independent prognostic indicators in patients with inoperable colorectal cancer receiving chemotherapy within the context of randomised phase III clinical trials. Patients with a high baseline global QoL have a 1-year survival that is almost double that of patients with a score below the median value (72.5% versus 38.3%, $P < 0.00001$). The relationship between QoL and survival has been documented in other cancer types [9–14,26].

However, the causal relationship between QoL and survival remains enigmatic. QoL may reflect an accurate perception of the severity of the underlying disease, which may not always be apparent in such crude measurements as tumour burden. In fact, a number of studies have suggested that QoL is superior to measuring tumour burden in assessing prognosis. Earlam found that physical QoL score as assessed by the Rotterdam Symptom Checklist predicted overall survival in patients with colorectal liver metastases receiving best supportive care alone [27]. The extent of liver metastases did not influence survival. Other studies that found QoL to be an independent predictor of survival, failed to find a significant relationship between survival and number of metastatic sites [26], or disease extent [11,28]. It is conceivable that tumour-related products such as cytokines and paraendocrine products are a better reflection of aggression than lesion size *per se*, and that these factors impact on a patient's QoL more significantly than tumour burden.

The possibility that QoL has a direct influence on tumour behaviour and survival has been proposed by some authors [9,14]. Watson and colleagues found a significant effect on breast cancer survival in a large cohort study. A helpless attitude and a high score for depression were predictive of poorer survival [29]. There are also a small number of 'intervention' studies, that suggest that improvement in QoL or coping mechanisms may have an influence on survival [30–33]. However, recently published data failed to support the treatment method developed by Spiegel [34]. In this Canadian study, 235 women with metastatic breast cancer were randomised on a 2:1 basis between 'supportive-expressive' group therapy and the control arm who did not receive such therapy. The authors found no significant difference in survival between the two arms. However, the findings of Watson and colleagues showing a modest impact of psychological response on survival in a large cohort ($n = 586$) suggests that the Goodwin study may have been underpowered. Clearly further research is required to establish the role of psychological intervention and survival in cancer patients.

A third possibility is that the patients' QoL has a direct influence on their adherence to therapy, which in itself may influence survival. For example, Andreyev and colleagues reported that, in patients with inoperable gastrointestinal malignancies, weight loss correlated with shorter failure-free survival and overall survival, decreased response rate and a poorer QoL [35]. They found that on average, patients with weight loss received 1 month (18%) less chemotherapy. This appeared to be related to more frequent and more severe dose-limiting toxicity. Several investigators have explored the possibility that both parenteral [36–38] and enteral [39,40] dietary supplementation may improve survival in cancer patients. Unfortunately, many of these studies are seriously flawed, and this interpretation remains unproven.

In the final multivariate model presented, QoL, a patient-based symptom/functioning measure, appears to be a stronger predictor of overall survival than PS, a clinician-based measure. When interpreting the results, it is important to remember that there is interaction between several of the prognostic factors, which may render previously significant factors in the baseline multivariate model non-significant in the final analysis. This is because of competing risks between prognostic factors that measure similar indices. The QoL questionnaire will measure aspects of patients' well-being and there may well be an interaction between these QoL factors and those that are measured by PS. In this study, when the baseline multivariate analysis was re-run with global QoL, PS was no longer an independent prognostic variable for survival, whilst global QoL was highly significant. However, this patient cohort was preselected with regard to PS, with 98% patients being of PS 0–2. It is feasible that, if patients of all PS levels were included, performance status may have remained

an important independent prognostic factor in the final multivariate model. However, other studies have suggested that QoL may indeed be a superior indicator of survival than PS. Ganz reported a significant relationship between QoL, as measured by the Functional Living Index-Cancer (FLIC) score, in 40 patients with metastatic non-small cell lung cancer (NSCLC) [26]. Karnofsky PS, however, did not significantly predict survival in their study. In a similar cohort of patients, Kaasa again found no significant relationship between PS and survival, despite QoL remaining an independent prognostic factor [11]. Other studies have demonstrated that QoL scores remain significant prognostic indicators, even after controlling for PS [10,28]. The differences in the ability of QoL and PS to predict survival may have a number of explanations. PS is a rather crude measurement, based on the general activity of the patient, whereas QoL measurements are generally much more sophisticated tools, that examine several aspects of patients' health and emotional status. More importantly, PS is an objective measurement imposed by the health professional, in contrast to the patient-based subjective measurement of QoL, which is arguably a more accurate reflection of general well-being.

Many of the issues surrounding QoL data and survival remain elusive. Whether QoL is simply a highly sensitive measure of patients' state of health that is not picked up by routine history taking, or whether it impacts on several dimensions of patients' self-care and their ability to tolerate chemotherapy, remains unclear. What is clear from this study, however, is that QoL measurements appear to be extremely sensitive tools in predicting survival in patients with colorectal cancer. Their inclusion into the vast majority of study protocols reflects the generally held belief of their value. Yet baseline QoL is not routinely presented in the demographic data of published work. For patient cohorts to be regarded equal with regards to baseline demographic factors, the inclusion of baseline QoL is arguably essential, given the highly significant difference in survival described in this study. This inclusion would facilitate comparisons not only within randomised trials, but also between studies. Further work is required to fully understand the causal relationships between QoL and survival, and which individual QoL domains are important, but its inclusion into demographic data should now be routine.

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