Hope, optimism and survival in a randomized trial of chemotherapy for metastatic colorectal cancer

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Abstract

Purpose: Psychological responses to cancer are widely believed to affect survival. We investigated associations between hope, optimism, anxiety, depression, health utility and survival in patients starting first line chemotherapy for metastatic colorectal cancer.

Methods: 429 subjects with metastatic colorectal cancer in a randomised controlled trial of chemotherapy, completed baseline questionnaires assessing: hopefulness, optimism, anxiety and depression and health utility. Hazard ratios (HR) and *P*-values were calculated with Cox models for overall survival (OS) and progression-free survival (PFS) in univariable and multivariable analyses.

Results: Median follow-up was 31 months. Univariable analyses showed that OS was associated negatively with depression (HR 2.04, *P<0.001*), and positively with health utility (HR 0.56, *P<0.001*) and hopefulness (HR 0.75, *P=0.013*). In multivariable analysis, OS was also associated negatively with depression (HR 1.72, *P<0.001*), and positively with health utility (HR 0.73, *P=0.014*), but *not* with optimism, anxiety or hopefulness. PFS was *not* associated with hope, optimism, anxiety or depression in any analyses.

Conclusions: Depression and health utility, but not optimism, hope, or anxiety were associated with survival after controlling for known prognostic factors in patients with advanced colorectal cancer. Further research is required to understand the nature of the relationship between depression and survival. If a causal mechanism is identified, this may lead to interventional possibilities.

Key Words: Hope, Optimism, Colorectal Cancer, Survival, Health Utility, Depression

Introduction

Advanced colorectal cancer and its treatments are associated with physical symptoms and side-effects, including bowel, bladder and sexual dysfunction, pain, fatigue and nausea [1]. These impact on the person's emotional and psychological state and adversely affect social, occupational and relationship functioning [2]. Adopting 'a positive attitude' is widely believed by patients to influence survival and is a way of taking control [3]. However, research about the relationship between psychological factors and cancer survival has yielded inconsistent results and has been fraught with methodological problems [4]. The main limitations have included samples that were small and/or unrepresentative; failure to control for major potential confounders such as the type of cancer, histological grade, stage of disease, performance status or age; and, the use poorly defined or measured psychological constructs.

Two possible conceptualisations of "being positive" are dispositional optimism and hope. Dispositional optimism has been defined as the global expectation that good things will be plentiful in the future and bad things scarce [5]. Hopefulness is a related but distinct concept. Agency is the core distinction between optimism and hope. This sense of agency (control over one's destiny) seems inextricably linked to the feeling of hope in cancer patients [6]. Hope has been defined in this study as "the perception that one can reach one's desired goals" [7]. Using this definition, it may be expected that patients who hope for longer survival may pursue life-prolonging treatments more vigorously and be more vigilant about self-care activities, such as diet, exercise and managing treatment side effects. There is emerging research demonstrating a link between self-care activities and colorectal cancer survival [8]. Whether or not psychological state is implicated, remains to be determined.

The purpose of this study was to prospectively determine whether baseline optimism and hope were associated with overall survival (OS), progression free survival (PFS) and objective tumour response (OTR), after adjustment for known prognostic factors in patients having first line chemotherapy for advanced colorectal cancer in a phase III trial comparing three chemotherapy regimens. The primary objective, specified a priori, was to determine whether baseline measures of optimism and/or hope were predictive of OS, alone or after adjustment for other prognostic factors, including anxiety, depression, and health utility. Secondary objectives were to determine if baseline measures of optimism and/or hope were predictive of progression-free survival or objective tumour response, before and after adjustment for other prognostic factors.

Materials and Methods

This study was a prospectively planned sub-study within the phase III MAX trial [9].

Patient eligibility criteria

Eligible patients were all those participating in the MAX trial with sufficient English to complete the questionnaires. The inclusion criteria were age ≥18 years, histological diagnosis of colorectal adenocarcinoma, unresectable metastatic disease, suitable for capecitabine monotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and life expectancy of at least 12 weeks. The exclusion criteria were: uncontrolled clinically significant cardiac disease, hypertension, arrhythmias or angina pectoris, acute myocardial infarction or cerebrovascular accident, regular use of aspirin >325 mg/day or NSAIDs, CNS metastases, active bleeding disorders, recent major surgical procedure, serious non-healing wound, ulcer or bone fracture, 24-hour urinary protein >2g/24 hours,

pregnancy, prior history of other malignancy. All participants provided written informed consent and all participating sites had ethics approval for the study.

Study design

In the MAX trial, participants were randomised to receive: capecitabine (C); capecitabine plus bevacizumab (CB); or capecitabine, bevacizumab and mitomycin C (CBM) [9]. This study found that adding bevacizumab to capecitabine, with or without mitomycin, significantly improved PFS, but not OS. Patients completed validated measures at baseline (before randomisation for the MAX trial) to assess optimism, hopefulness, anxiety, depression and health utility. Patients were followed for a minimum of 12 months. The median follow-up was 31 months. A previous publication has further methodological details [9].

Measures

Patients were asked to complete 5 scales of hope or optimism.

Optimism was measured by the Life Orientation Test (LOT) [10]. The LOT comprises 10 items: optimistic (3 items); pessimistic (3 items) and four filler items with five-point response scale (0='disagree strongly' to 4='agree strongly'). The averaged total score ranged from 0 to 4 with a high score representing greater optimism.

Hopefulness was measured by the State Hope Scale [7]. It has 6 items comprising 2 subscales: pathway and agency (3 items each). 'Pathways thinking' signifies one's perceived capabilities at generating workable routes to desired goals. 'Agency thinking' is the perceived capacity for initiating and maintaining the actions necessary to reach a goal. The response scale ranges from 0 "definitely false" to 8

"definitely true". The average total score ranges from 0 (least hopefulness) to 8 (greatest hopefulness).

Anxiety and depression was assessed using the 14-item Hospital Anxiety and Depression Scale (HADS) with 7 items in each of the anxiety and depression subscales [11]. The total score for each subscale ranges from 0 (least) to 21 (greatest) anxiety or depression respectively. A score of 11–21 was classified as a probable case and a score of 8–10 as a possible case.

Health utility, a measure of overall quality of life suitable for health economic evaluations, was measured with the EuroQOL-5D (EQ-5D) comprised of 5 items and giving a utility score ranging from 0 (worst possible) to 1 (perfect health) [12].

Response and progression were assessed according to version 1.0 of the Response Evaluation Criteria in Solid Tumors (RECIST, standard international criteria for classifying the response to treatment of tumours evident on imaging as complete response, partial response, stable disease or disease progression) [13].

Statistical Analysis

Primary analyses assessed the prognostic significance of optimism, hopefulness, anxiety, depression and quality of life by dichotomising variables according to cutpoints defined *a priori*. Established cutpoints were used where available; otherwise the median was used to divide the cohort into subgroups of similar size..

Associations with OS and PFS were determined with Cox models to calculate hazard ratios, 95% confidence intervals and *P*-values to quantify the effects of

variables on the hazard of death (instantaneous rate of death per unit time) in univariable and multivariable analyses. The Kaplan Meier method was used to estimate median survival times. Multivariable models were designed to determine the prognostic significance of the psychological factors after accounting for traditional prognostic factors. These models included baseline characteristics that were significant predictors of outcome in our main trial analyses [9], the health utility score, and the psychological factors.

All statistical inferences were based on two-sided p-values of 0.05 with no adjustment for multiple comparisons. All analyses were performed with SAS (version 9.2; SAS Institute, Cary, NC). The sample size was determined by the requirements of the randomized trial within which the study was nested, which provided over 90% power to detect a 33% relative reduction in the hazard for OS for a binary characteristic with a prevalence of 50%.

Results

Of the 471 participants in the MAX trial, 429 (88%) completed at least one of the psychological measures at baseline (Supplementary Figure 1).

Baseline characteristics of the participants are summarised in Table 1 and were well balanced between the randomly allocated treatment groups (data not shown, but previously published [9]). The majority of participants had good performance status and good health-related quality of life. Scores were indicative of probable clinical depression in 5%, and of probable clinical anxiety in 12%. Distributions of baseline scores for the psychological factors are summarised in Table 2.

There were significant correlations among all of the psychological factors at baseline (see Table 3). There was a strong negative correlation between hope and depression, a moderate positive correlation between anxiety and depression, and there were moderate negative correlations between health utility and both anxiety and depression.

Predictors of PFS and OS in univariable analysis are summarised in Table 4 and Table 5. Health utility was the only psychological variable associated with PFS; hope, optimism, anxiety and depression were not significantly associated with PFS. Psychological predictors of OS in univariable analyses included health utility, depression and hopefulness, but not anxiety or optimism (Table 5).

In multivariable analysis including traditional prognostic factors, the only psychological factors that were independent significant predictors of OS were a HADS depression score of 8 or higher (HR 1.72, 95% CI 12.3 to 2.38, *P<.001*) and EQ-5D health utility score of 0.8 or higher (HR 0.73, 95% CI 0.57 to 0.94, *P =.014*). Table 6 shows predictors that were significant in the multivariable model. No psychological factors were independently significant predictors of progression free survival (data not shown).

Discussion

After controlling for known prognostic factors, patient reported scores for depression and health utility were significant independent predictors of OS, whereas hopefulness, optimism and anxiety were not. None of these psychological factors were significant predictors of PFS. These findings add to the growing body of evidence [14-17] that both depression and quality of life assessed prior to treatment may influence OS after controlling for known clinical prognostic factors.

Chida and colleagues conducted a systematic review investigating the influence of psychological factors on cancer survival [14]. Whilst acknowledging publication bias, they concluded that stressful life events, unfavourable coping styles (such as helplessness-hopelessness), depression, and poor quality of life were related to poorer survival and higher mortality. However, others note significant flaws with individual studies, rendering interpretation difficult [4,18]. A systematic review of the influence of psychological coping and adjustment on cancer survival with more stringent inclusion criteria found most of this research has focused on fighting spirit and helplessness-hopelessness and the majority reported no significant associations with survival [19]. Conversely, high quality meta-analyses investigating the influence of baseline quality of life on cancer survival have consistently shown that quality of life provides additional prognostic value after adjusting for known prognostic clinical factors, both across cancer types [15,17] and in patients with advanced colorectal cancer, specifically [20,21]. A recent meta-analysis investigating depression and cancer survival that excluded methodologically flawed studies concluded that baseline depression had a small but significant influence on survival that did not diminish after controlling for other prognostic factors [16]. However, research about the influence of positive psychological states on cancer survival remains contentious [4].

Common methodological flaws have hindered previous attempts to determine the effects of psychological factors on survival [4,22]. These flaws include: small or heterogeneous study populations, failing to control for potential confounders either statistically or by sampling; follow-up that is too short; and the use of inadequately defined or measured psychological constructs. In contrast, the current study assessed psychological constructs shortly after diagnosis of metastatic disease using reliable and valid instruments on a tightly defined sample recruited at the same point

in their illness trajectory with a long follow up and statistical adjustment for known prognostic factors.

These findings do not support the notion that optimism influences cancer survival. There have been inconsistent results in research investigating the relationship between optimism and cancer survival, most likely due to methodological flaws described above. In a study of patients with different types of cancer, no independent effects of optimism or pessimism on survival were found [23]. Another study examining patients with metastatic melanoma reported that optimism was associated with prolonged survival, however optimism was assessed by a single item asking the patient their perceived aim of treatment [24]. Responses to this item may be a reflection of communications from the doctor about treatments and prognosis, hence not an accurate measure of dispositional optimism. A long-term study of lung cancer patients found no association between pessimism and survival after adjusting for confounders [25]. Another study of patients with head and neck cancer found that dispositional optimism was predictive for 1 year survival after controlling for prognostic factors [26]. This study was based on a heterogeneous sample which included oral, pharyngeal and laryngeal cancers with stages ranging from I to IV and different treatment modalities. The authors acknowledge two serious limitations. First, sample heterogeneity and fluctuations in timing of the questionnaire administration with respect to the receipt of test results may have influenced optimism ratings. Second, potentially important predictive factors were omitted including performance status, socio-economic status, smoking status and biologic markers. Any of these may co-vary with optimism. In our previous study, we investigated the relationship between optimism and survival in a large, homogeneous sample of patients with advanced non-small cell lung cancer who were recruited at the same point in their illness trajectory [22]. Using validated measures and a long follow-up period, we found no association between pre-treatment optimism and PFS or OS after

controlling for the known prognostic factors. The current study displayed a similar level of scientific rigour. When taking into account the methodological rigor of each study, the weight of current evidence suggests that level of optimism does not play a role in cancer survival.

To our knowledge, this is the first study to investigate the relationship between hope and cancer survival. While there was a significant relationship between hopefulness and OS in univariable analysis, this relationship was not sustained in the multivariable analysis accounting for known traditional prognostic factors, health utility and depression. A potential reason for this is the strong negative relationship between hope and depression (r=-0.63). The HADS was selected for this research because it does not include somatic items, such as sleep problems, fatigue, or appetite loss, which are all indicators of depression [27]. In a cancer population, these items may just reflect the symptoms and side-effects associated with advanced cancer and treatments. The depression subscale of HADS focuses on the anhedonic aspects of depression, including feelings of sadness and loss of pleasure or interest in activities, recognising that physical symptoms may affect these feelings [2]. High anhedonic depression is incompatible with feeling a strong sense of agency to achieve one's goals, the definition used for hope. These constructs are clearly inversely related.

The question is: does actively treating a patient's depression not only improve their emotional well-being but might it also extend their life?. Randomized controlled trials testing the effects of psychotherapeutic intervention on cancer survival have been mixed [28]. Indeed, Coyne and colleagues presented a compelling argument to support their conclusion that "no randomized clinical trial designed with survival as a primary endpoint and in which psychotherapy was not confounded with medical care has yielded a positive result" [28]. They agree that improved adherence to medical

advice and self-care is a plausible mechanism by which depression might influence survival, and two trials [29,30] lend modest support to this assertion. Obviously, this is speculative.

Placebo-controlled trials of antidepressant drugs suggest that they can improve depression and quality of life in patients with advanced cancer and significantly depressed mood or anhedonia [31] but not in those with milder symptoms of depression [32]. Survival analyses in these trials did not suggest any benefit of antidepressant drugs. To date, research, including this study, only demonstrate an association between depression and survival not that depression *influences* survival. Further research is required to understand the nature of the relationship between depression and survival. If there appears to be a causal link, this may lead to the potential for intervention.

The main limitation of this study is its observational design: this allows strong inferences about association, but not about causality. While eligibility criteria was tight and a number of prognostic indicators were controlled for in the analyses, there was still the potential for the baseline assessment to be confounded with prognosis. A patient's general health status or their physician's communication relating to prognosis or potential treatment efficacy may have influenced responses to psychological assessments. In addtion, our findings are confined to patients having first line chemotherapy for colorectal cancer. Confirmation of our findings in other settings with alternative instruments is needed.

Conclusions

This is the largest and most methodologically robust prospective study of the relationship between hope, optimism and survival in advanced cancer patients. We used instruments for measuring hope, optimism and depression which are the best

validated and available for the cancer setting in a large, homogeneous sample of people with metastatic colorectal cancer. The concept, instruments, data collection and analysis were planned a priori. The findings support previous research which suggests that lower levels of depression and higher quality of life predict longer OS independent of other known prognostic factors. This relationship did not hold for progression free survival. Optimism was not associated with OS or PFS. Hopefulness was negatively correlated with depression, and was associated with OS when assessed alone but not after accounting for other known prognostic factors.

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Conflict of interest

None of the authors has any conflict of interest with respect to this study. The study sponsors had no involvement in any aspect of the conduct of this research. The authors had full control of all primary data and agree to allow the journal to review the data if requested.

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Table 1: Baseline characteristics (N=429)

	Total n= 429
Performance status (ECOG)	
0	245 (57%)
1	162 (38%)
2	22 (5%)
Age in years (median, range)	67 (32-86)
Male	271 (63%)
Primary tumor resected	338 (79%)
Liver metastases	324 (76%)
Prior Radiotherapy	55 (13%)
Prior Chemotherapy	93 (22%)
EQ-5D utility	
< 0.8	242 (57%)
≥ 0.8	180 (43%)
HADS anxiety	
< 8	291 (69%)
8 - 10	80 (19%)
11 - 15	39 (9%)
16+	11 (3%)
HADS depression	
< 8	360 (86%)
8 - 10	40 (10%)
11 - 15	15 (4%)
16+	6 (1%)
LOTS optimism	
< 2.5	150 (35)
≥ 2.5	274 (65)
SHS Hopefulness	
< 6	160 (38)
≥ 6	263 (62)

Data are n (%) or median (range)

Table 2: Baseline scores for psychological factors.

Variable	N	Mean	Median	Q1	Q3	Min	Max
EQ-5D utility (0 to 1)	422	0.75	0.80	0.69	0.88	0	1
HADS anxiety (0 to 21)	421	5.8	5	3	8	0	20
HADS depression (0 to 21)	421	3.8	3	1	6	0	18
LOTS optimism (0 to 4)	424	2.7	2.7	2.2	3.2	0.7	4
SHS Hopefulness (0 to 8)	423	6.0	6.3	5.2	7.2	1.0	8

Notes: Q1 & Q3 are the first and third quartiles, i.e. 25% of observed values are below Q1 and 25% are above Q. Between Q1 and Q3 are the 'middle fifty.'

Table 3: Spearman rank correlations among psychological factors at baseline.

	Optimism	Anxiety	Depression	EQ-5D utility
Hope	0.34	-0.43	-0.63	0.39
Optimism		-0.35	-0.35	0.22
Anxiety			0.51	-0.45
Depression				-0.48

$p < 0.0001$ for all correlations

Table 4: Progression Free Survival - Univariable models

NOTE: the comparator for each row is the level indicated first in brackets, except for treatment .

Variable	With characteristic n (%)	Median survival time (months) without characteristic	with characteristic	HR (95% CI) with characteristic	P
Treatment					
C (reference)	145 (33)		6		
CB	146 (33)		9	0.59 (0.46, 0.75)	<0.001
CBM	147 (34)		8	0.56 (0.44, 0.71)	<0.001
Conventional prognostic factors					
Age (<60 vs. 60+)	321 (73)	8	7	0.94 (0.76, 1.18)	0.608
Gender (F vs. M)	277 (63)	7	7	0.94 (0.76, 1.15)	0.530
PS (0 vs. 1-2)	186 (42)	8	6	1.57 (1.29, 1.92)	<0.001
Liver metastases (N vs. Y)	331 (76)	7	7	1.18 (0.94, 1.48)	0.158
Haemoglobin (12+ vs. <12)	146 (33)	7	7	1.19 (0.97, 1.46)	0.097
ALP (<140 vs. 140+)	162 (37)	8	6	1.45 (1.19, 1.78)	<0.001
CEA (<30 vs. 30+)	205 (48)	7	7	1.28 (1.05, 1.57)	0.014
Primary Tumor Resected (N vs. Y)	346 (79)	7	8	0.71 (0.56, 0.90)	0.004
Bilirubin (<14 vs. 14+)	79 (18)	7	7	1.22 (0.95, 1.57)	0.116
Number of metastatic sites (<2 vs. 2+)	181 (41)	8	7	1.32 (1.08, 1.61)	0.007
Patient rated measures					
EQ-5D utility (<0.8 vs. 0.8+)	180 (43)	7	8	0.76 (0.62, 0.93)	0.007
HADS anxiety (<8 vs. 8+)	130 (31)	7	7	1.05 (0.85, 1.32)	0.616
HADS depression (<8 vs. 8+)	61 (15)	7	6	1.21 (0.91, 1.59)	0.202
LOTS optimism (<2.5 vs. 2.5+)	274 (65)	7	7	1.03 (0.84, 1.27)	0.786
SHS Hopefulness (<6 vs. 6+)	263 (62)	7	8	0.90 (0.73, 1.10)	0.312

Notes: HADS scores of 8 or more signifying possible or probable depression or anxiety; optimism scores of 2.5 or more signifying higher optimism and hopefulness scores of 6 or more signifying higher hopefulness. C – capecitabine, CB – capecitabine with bevacizumab, CBM – capecitabine with bevacizumab and mitomycin, PS – performanace status, ALP – alkaline phosphatase, CEA – carcinoembryonic antigen.

Table 5: Overall survival - Univariable models

NOTE: the comparator is the level indicated first in the brackets except for Treatment

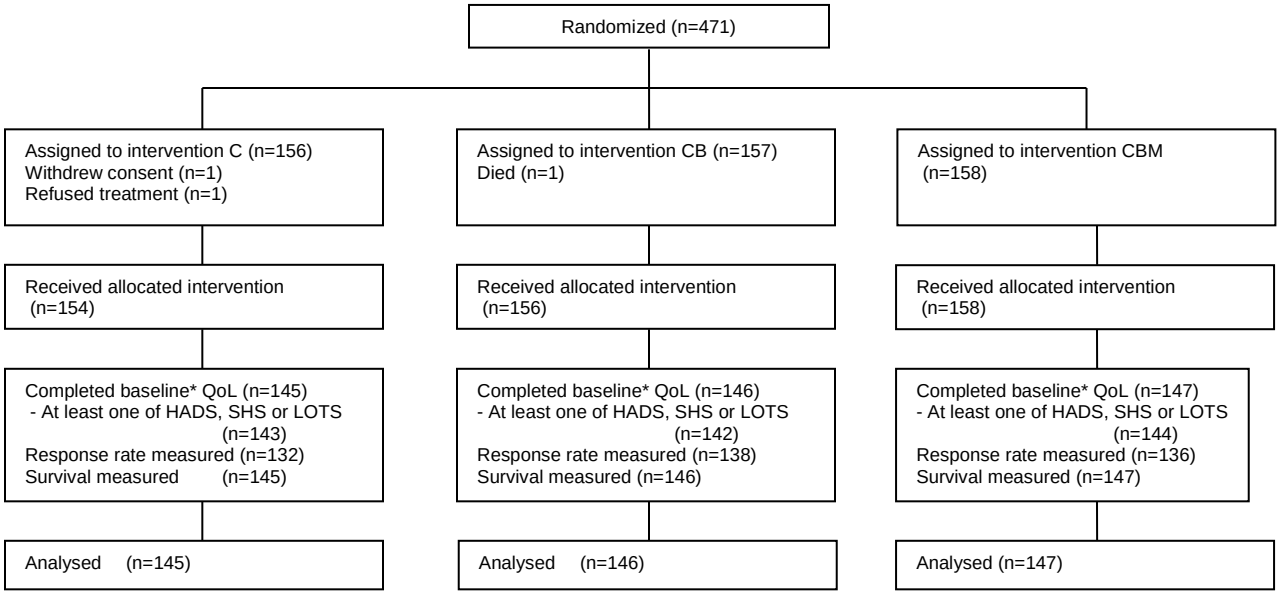
Variable	With characteristic n (%)	Median survival time (months) without characteristic	Median survival time (months) with characteristic	HR (95% CI)	P
Treatment					
C (reference)	145 (33)		19	1.00	
CB	146 (33)		20	0.79 (0.61, 1.03)	0.078
CBM	147 (34)		16	0.97 (0.75, 1.26)	0.841
Conventional prognostic factors					
Age (<60 vs. 60+)	321 (73)	21	17	1.28 (1.00, 1.64)	0.047
Gender (F vs. M)	277 (63)	17	20	0.86 (0.69, 1.07)	0.179
PS (0 vs. 1-2)	186 (42)	22	13	2.09 (1.68, 2.60)	<0.001
Liver metastases (N vs. Y)	331 (76)	22	17	1.20 (0.93, 1.56)	0.157
Haemoglobin (12+ vs. <12)	146 (33)	21	13	1.69 (1.35, 2.11)	<0.001
ALP (<140 vs. 140+)	162 (37)	22	12	1.87 (1.50, 2.32)	<0.001
CEA (<30 vs. 30+)	205 (48)	20	16	1.24 (1.00, 1.54)	0.055
Neutrophils (<8 vs. 8+)	346 (79)	20	9	1.89 (1.41, 2.52)	<0.001
Prior Radiotherapy (N vs. Y)	79 (18)	18	16	1.28 (0.94, 1.74)	0.125
Primary Tumor Resected (N vs. Y)	181 (41)	13	20	0.62 (0.48, 0.80)	<0.001
Patient rated measures					
EQ-5D utility (<0.8 vs. 0.8+)	180 (43)	16	23	0.56 (0.45, 0.71)	<0.001
HADS anxiety (<8 vs. 8+)	130 (31)	19	17	1.06 (0.84, 1.34)	0.634
HADS depression (<8 vs. 8+)	61 (15)	20	11	2.04 (1.52, 2.70)	<0.001
LOTS optimism (<2.5 vs. 2.5+)	274 (65)	17	18	0.98 (0.78, 1.23)	0.871
SHS Hopefulness (<6 vs. 6+)	263 (62)	15	20	0.75 (0.60, 0.94)	0.013

C – capecitabine, CB – capecitabine with bevacizumab, CBM – capecitabine with bevacizumab and mitomycin, PS – performanace status, ALP – alkaline phosphatase, CEA – carcinoembryonic antigen.

Table 6: Overall Survival - multivariable model including traditional factors significant in the trial's original analysis (N= 407)

Variable	Characteristic	No. (%)	HR	95% CI for HR	P
Treatment group	C	134 (33)	1.00		
	CB	136 (33)	0.80	(0.60,1.05)	0.107
	CBM	137 (34)	0.94	(0.72,1.23)	0.662
Performance status	≥ 1	172 (42)	1.62	(1.29,2.05)	<0.001
Neutrophils ($x10^9$/L)	≥ 8	58 (14)	1.33	(0.96,1.85)	0.083
Alkaline phosphatase (U/L)	≥ 140	151 (37)	1.65	(1.30,2.09)	<0.001
Prior radiotherapy	Yes	321 (79)	1.54	(1.10,2.15)	0.011
Primary Tumor Resected	Yes	321 (79)	0.79	(0.61,1.03)	0.086
HADS Depression	≥ 8	58 (14)	1.72	(1.23, 2.38)	<0.001
EQ-5D utility	≥ 0.8	173 (43)	0.73	(0.57,0.94)	0.014

Supplementary Figure 1: Consort Diagram



Notes: There were 438 patients who completed at least one baseline QoL for EQ-5D, HADS, LOT or SHS. There were 429 patients who completed at least one of HADS, LOT or SHS. The numbers of patients completing each questionnaire were: HADS = 421, LOT = 424, SHS = 423