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Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer

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ABSTRACT

This international study aimed to test the measurement properties of the updated European Organisation for Research and Treatment of Cancer (EORTC) questionnaire module for colorectal cancer, the QLQ-CR29.

The QLQ-CR29 was administered with the QLQ-C30, core questionnaire, to 351 patients from seven countries. Questionnaire scaling and reliability were established and clinical and psychometric validity examined. Patient acceptability and understanding were assessed with a debriefing questionnaire.

Multi-trait scaling analyses and face validity refined the module to four scales assessing urinary frequency, faecal seepage, stool consistency and body image and single items assessing other common problems following treatment for colorectal cancer. Scales distinguished between clinically distinct groups of patients and did not correlate with QLQ-C30 scales, demonstrating construct validity. The QLQ-CR29 scores were reproducible over time in stable health.

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The EORTC QLQ-CR29 demonstrates sufficient validity and reliability to support its use to supplement the EORTC QLQ-C30 to assess patient-reported outcomes during treatment for colorectal cancer in clinical trials and other settings.

1. Introduction

Colorectal cancer is the second commonest cause of cancer-related deaths in the developed world. Surgical resection provides the best hope of cure, and a modest additional survival benefit can be gained from adjuvant chemotherapy.[1] Preoperative radiotherapy for rectal cancer has been shown to improve local disease control.[2] In trials of treatment for colorectal cancer standard outcomes include toxicity scores, surgical-related morbidity, local recurrence rates, disease free survival and overall survival, but over the past decade there had been an increasing focus on supplementing clinical outcomes with outcomes reported by the patients themselves. Assessing the patient's perspective of outcome can be achieved with patient-reported outcome measures (PROMs) including health-related quality of life (HRQL) questionnaires. Generic tools to assess HRQL in cancer patients have been developed and these include the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the Functional Assessment of Cancer Therapy General scale (FACT-G).[3,4] Both core measures may be supplemented with disease specific modules.[5,6] These assess important issues such as bowel, bladder and sexual dysfunction and problems relating to stoma formation.

The EORTC QLQ-CR38 was developed originally in the Netherlands and it has been widely used in many trials and research settings.[5] Although some psychometric data have been published, it was never formally validated in an international setting.[5,7,8] Work to revise the QLQ-CR38 began a few years ago and a shorter questionnaire, the QLQ-CR29, was developed.[9] The aims of this present study are to examine the psychometric properties of the EORTC QLQ-CR29 in an international field study and to validate it for use in clinical trials in patients with colorectal cancer.

2. Methods

2.1. Patients

This multi-centre study opened in March 2007 and closed in October 2008. Participants over the age of 18 years, with a histological diagnosis of adenocarcinoma of the colon or rectum were included and those with concurrent malignancy, or a psychological or linguistic impairment that hampered completion of the questionnaires were excluded. Ethics committee approval and written informed consent were obtained and the protocol was approved by the EORTC Quality of Life Group.

2.2. Questionnaires

The participants completed the EORTC QLQ-C30 (version 3.0) and QLQ-CR29 at all assessment points. The QLQ-CR29 contains 29 items, and is described in detail elsewhere.[9] Briefly, there are 18 items addressing gastrointestinal symptoms, pain and problems with micturition, and there are separate scales for the participants with or without a stoma and separate items addressing sexual function for men and women. The response categories for each item are the same as those used in the QLQ-C30. The module was translated according to EORTC guidelines into six languages for the purpose of this validation study.[10] The core questionnaire, the EORTC QLQ-C30, is an extensively validated questionnaire assessing functional and symptom aspects of HRQL.[3,11] Responses to the core questionnaire and the QLQ-CR29 were linearly converted into 0–100 scores using standard EORTC guidelines.[12] The participants also completed a short debriefing questionnaire that recorded the time taken to complete both instruments and it asked the participants to report whether they needed help in completing the questionnaires and queried if any of the items appeared confusing, difficult to answer or were upsetting.

2.3. Timing of assessments

The participants completed the questionnaires at selected time points according to the treatment schedule. Six groups were created for this validation study to represent a range of patients with colorectal cancer, treatments and different timings of the treatment (Table 1). The participants in Groups 1, 2, 3 and 5 completed the HRQL assessments on a single occasion and participants in Groups 4 and 6 completed questionnaires twice, before and after treatment to assess sensitivity to change over time. In addition, 70 participants from all groups were asked to complete a second HRQL assessment between 7 and 14 d after the first set of questionnaires (to assess test–retest reliability). These participants also recorded whether they have experienced a change in health status during this time period.

2.4. Statistical analysis

Questionnaire responses were initially analysed to establish the scale structure of the QLQ-CR29. Tests of clinical and psychometric validity were then performed using the finalised scales and single items.

2.4.1. Defining the HRQL scales and items in the QLQ-CR29

The QLQ-CR29 was created with six hypothesised scales (micturition, pain, faecal incontinence, defaecation problems, anxiety and body image) and 11 single items.[9] Multi-trait scaling was used to test whether the items of the QLQ-CR29 fitted with the proposed scale structure. Item convergent validity was defined as item-scale correlations of 0.40 or greater (corrected for overlap). Item discriminant validity was indicated when an item had a higher correlation with its own scale (cor-

Table 1 – Inclusion criteria for the validation study of the EORTC QLQ-CR29.

	Inclusion criteria	Timing of completion of questionnaires
Group 1	Previous hemi-colectomy or colectomy (right/ transverse/left/sigmoid/subtotal) Previous anterior resection No stoma Not receiving adjuvant chemotherapy	Within 12 months of surgery
Group 2	Previous hemi-colectomy or colectomy (right/ transverse/left/sigmoid/subtotal) Previous anterior resection No stoma Receiving or within 2 weeks of receiving adjuvant chemotherapy	Within 12 months of surgery, during or within two weeks of receiving a cycle of chemotherapy
Group 3	Rectal cancer Receiving pre-operative radiotherapy	Before surgery, during or within 2 weeks of receiving radiotherapy
Group 4	Anterior resection Temporary stoma May be receiving chemotherapy	First assessment – after surgery with a stoma Second assessment – within 2 years of stoma closure
Group 5	Abdominal perineal resection Permanent stoma May be receiving chemotherapy	Within 60 months of surgery
Group 6	Treatment with palliative intent May have undergone surgery	First assessment – whilst receiving palliative chemotherapy or within 2 weeks of cycle completion Second assessment – 3 months from First assessment

rected for overlap) than with another scale. Scaling errors were considered to occur when items consistently correlated more highly with another scale or did not correlate with any of the hypothesised scales. On the basis of the scaling results, the scale structure of the QLQ-CR29 was revised and the scaling properties were re-examined.

2.4.2. *Reliability*

Internal consistency is the extent to which the items within a scale are interrelated. This was measured using Cronbach's alpha coefficient with estimates of a magnitude of >0.70 being considered acceptable for group comparisons.[13]

2.4.3. *Reproducibility*

The test–retest reliability (reproducibility) of the QLQ-CR29 was assessed using intraclass correlations between the first and second test–retest assessments (7–14 d apart) in patients reporting stable health.

2.4.4. *Validity*

Correlations between the scales and single items of both the QLQ-C30 and QLQ-CR29 were examined using Pearson's product moment correlation. Pearson's values of greater than 0.40 were considered highly correlated. It was anticipated that the scales in the new module would not be expected to relate to generic aspects of HRQL unless they addressed similar themes such as pain.

2.4.5. *Clinical validity*

Known group comparisons examined the extent to which the QLQ-CR29 scores were able to discriminate between subgroups of clinically distinct patients. The clinical parameter hypothesised to form mutually exclusive patient subgroups for comparison included the presence of a stoma (stoma versus no stoma) baseline treatment groups (potentially curative i.e. Groups 1–5 versus palliative i.e. Group 6) and baseline Karnofsky scores (<80 versus >80). The group differences were assessed using the Wilcoxon rank sum test.

2.4.6. *Responsiveness to change in clinical health status over time*

Sensitivity to change over time was examined in patients undergoing palliative chemotherapy (Group 6) and after closure of a temporary stoma (Group 4).

2.4.7. *Sample size calculation*

The sample size was planned before the start of the study and was based on the recommendation of Tabachnik and Fidell that for multivariate analysis techniques to obtain reliable estimates, the number of patient observations should be 10 times the number of variables in the model.[14] The minimum sample size required was, therefore, 290 participants and this was inflated to allow for attrition. All analyses were undertaken using STATA version 10.0 software (StataCorp LP, Texas, United States of America).

3. Results

3.1. *Patient characteristics, compliance rates and questionnaire feasibility*

Three hundred and fifty-one patients from seven countries were enrolled (Table 2). Baseline questionnaires were returned from all and the majority of patients (83%) completed the QLQ-C30 and QLQ-CR29 in less than 15 min, although 28% required some help with questionnaire completion. Debriefing questionnaires were completed by 344 (98%), and 14 (4%) reported that the sexual function items were not relevant. Another 36 (10%) reported that some questions were difficult to answer. No items were consistently selected as difficult

Table 2 – Clinical details for overall sample and for each study Group.

	Total sample $n = 351$	Group 1 $n = 60$	Group 2 $n = 86$	Group 3 $n = 31$	Group 4 $n = 53$	Group 5 $n = 45$	Group 6 $n = 76$
Mean age in years (SD)	65.0 (11.9)	66.5 (13.4)	62.6 (12.6)	63.8 (10.7)	66.6 (12.8)	68.1 (10.2)	64.2 (10.2)
Gender							
Male (%)	205 (58.4)	31 (51.7)	48 (55.8)	21 (67.7)	30 (56.6)	30 (66.7)	45 (59.2)
Nationality							
United Kingdom	125 (35.6)	33 (55.0)	27 (31.4)	2 (6.5)	31 (58.5)	26 (57.8)	6 (7.9)
France	66 (18.8)	0 (0.0)	14 (16.3)	17 (54.8)	2 (3.8)	4 (8.9)	29 (38.2)
Taiwan	57 (16.2)	4 (6.7)	22 (25.6)	5 (16.1)	5 (9.4)	2 (4.4)	19 (25.0)
Italy	49 (14.0)	17 (28.3)	14 (16.3)	3 (9.7)	6 (11.3)	2 (4.4)	7 (9.2)
Germany	44 (12.5)	6 (10.0)	9 (10.5)	1 (3.2)	9 (17.0)	4 (8.9)	15 (19.7)
Spain	7 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (15.6)	0 (0.0)
United States of America	3 (0.8)	0 (0.0)	0 (0.0)	3 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)
Cohabitation (%)							
Alone	60 (17.1)	7 (11.7)	9 (10.5)	8 (25.8)	17 (32.1)	5 (11.1)	14 (18.4)
With adults or family	290 (82.6)	53 (88.4)	77 (89.5)	23 (74.0)	36 (67.9)	40 (88.9)	61 (80.3)
Unknown	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Marital status (%)							
Single	19 (5.4)	4 (6.7)	3 (3.5)	2 (6.5)	5 (9.4)	0 (0.0)	5 (6.6)
Married	273 (77.8)	48 (80.0)	72 (83.7)	20 (64.5)	36 (67.9)	39 (86.7)	58 (76.3)
Divorced, widowed, separated	58 (16.5)	8 (13.3)	11 (12.8)	9 (29.0)	12 (22.6)	6 (13.3)	12 (15.8)
Unknown	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Education (%)							
Less than compulsory school	21 (6.0)	2 (3.3)	8 (9.3)	2 (6.5)	4 (7.5)	1 (2.2)	4 (5.2)
Compulsory school	183 (52.1)	36 (60.0)	36 (41.9)	16 (51.6)	28 (52.8)	29 (64.4)	38 (50.0)
Post-compulsory school	100 (28.5)	15 (25.0)	30 (34.9)	9 (29.0)	14 (26.4)	9 (20.0)	23 (30.0)
University level	42 (12.0)	7 (11.7)	12 (14.0)	4 (12.9)	6 (11.3)	4 (8.9)	9 (11.8)
Unknown	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	2 (4.4)	2 (2.6)
Employment (%)							
Full or part-time	93 (26.5)	17 (28.3)	23 (26.7)	9 (29.0)	14 (26.4)	11 (24.4)	19 (25.0)
Homemaker	28 (8.0)	8 (13.3)	5 (5.8)	5 (16.1)	1 (1.9)	2 (4.4)	7 (9.2)
Unemployed	15 (4.3)	0 (0.0)	6 (7.0)	1 (3.2)	2 (3.8)	2 (4.4)	4 (5.3)
Retired	200 (57.0)	33 (55.0)	49 (57.0)	13 (41.9)	33 (62.3)	27 (60.0)	45 (59.2)
Other	12 (3.4)	2 (3.3)	3 (3.5)	3 (9.7)	2 (3.8)	2 (4.4)	0 (0.0)
Unknown	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.2)	1 (1.3)
Karnofsky performance (%)							
<60	12 (3.4)	1 (1.7)	1 (1.2)	1 (3.2)	5 (9.4)	2 (4.4)	2 (2.6)
60–80	113 (32.2)	25 (41.7)	20 (23.3)	10 (32.2)	24 (45.3)	11 (24.4)	23 (30.3)
>80	214 (61.0)	30 (50.0)	63 (73.3)	20 (64.5)	20 (37.7)	31 (68.9)	50 (65.8)
Unknown	12 (3.4)	4 (6.7)	2 (2.3)	0 (0.0)	4 (7.5)	1 (2.2)	1 (1.3)
Stoma (%)							
Yes	116 (33.1)	0 (0.0)	0 (0.0)	0 (0.0)	53 (100.0)	45 (100.0)	18 (23.7)
Primary tumour (%)							
Right or transverse colon	80 (22.8)	23 (38.3)	35 (40.7)	0 (0.0)	0 (0.0)	0 (0.0)	20 (26.3)
Left or sigmoid colon	76 (21.7)	14 (23.3)	33 (38.4)	0 (0.0)	4 (7.6)	3 (6.7)	22 (29.0)
Recto-sigmoid colon	39 (11.1)	8 (13.3)	8 (9.3)	3 (9.7)	13 (24.5)	1 (2.2)	6 (7.9)
Rectum	154 (43.9)	15 (25.0)	9 (10.5)	28 (90.3)	36 (67.9)	41 (91.1)	27 (35.5)
Unknown	2 (0.6)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Tumour stage (%)							
Stage I	47 (13.4)	15 (25.0)	6 (7.0)	0 (0.0)	12 (22.6)	14 (31.1)	0 (0.0)
Stage II	75 (21.4)	21 (35.0)	23 (26.7)	0 (0.0)	13 (24.5)	18 (40.0)	0 (0.0)
Stage III	90 (25.6)	16 (26.7)	50 (58.1)	0 (0.0)	15 (28.3)	9 (20.0)	0 (0.0)
Stage IV	98 (27.9)	3 (5.0)	6 (7.0)	3 (9.7)	6 (11.3)	4 (8.9)	76 (100.0)
Unknown	41 (11.6)	5 (8.3)	1 (1.2)	28 (90.3)	7 (13.2)	0 (0.0)	0 (0.0)
Surgical access (%)							
Open	170 (48.4)	36 (60.0)	41 (47.7)	0 (0.0)	30 (56.6)	35 (77.8)	28 (36.8)
Laparoscopic	57 (16.2)	16 (26.7)	24 (27.9)	0 (0.0)	9 (17.0)	3 (6.7)	5 (6.6)
No surgery	43 (12.3)	0 (0.0)	0 (0.0)	31 (100.0)	0 (0.0)	0 (0.0)	12 (15.8)
Unknown	81 (23.1)	8 (13.3)	21 (24.4)	0 (0.0)	14 (26.4)	7 (15.6)	31 (40.8)

(*continued on next page*)

Table 2 – (*continued*)

	Total sample $n = 351$	Group 1 $n = 60$	Group 2 $n = 86$	Group 3 $n = 31$	Group 4 $n = 53$	Group 5 $n = 45$	Group 6 $n = 76$
Chemotherapy (%)							
Yes	239 (68.1)	0 (0.0)	86 (100.0)	26 (83.9)	24 (45.3)	29 (64.4)	74 (97.4)
Unknown	4 (1.1)	0 (0.0)	0 (0.0)	1 (3.2)	3 (5.7)	0 (0.0)	0 (0.0)
Radiotherapy (%)							
Yes	101 (28.8)	4 (6.7)	4 (4.6)	31 (100.0)	16 (30.2)	31 (68.9)	15 (19.7)
Unknown	9 (2.6)	1 (1.7)	2 (2.3)	0 (0.0)	2 (3.8)	1 (2.2)	3 (4.0)

except for sexual items ($n = 10$). At the baseline assessment there were 70 (0.7%) missing items from the QLQ-C30 and 217 (2.3%) from the QLQ-CR29. Missing data were mostly from the sexual items in the QLQ-CR29 (items 56, 57, 58 and 59).

3.2. *Defining the HRQL scales and items in the QLQ-CR29*

Each of the original hypothesised scales was modified based upon the scaling data and its clinical interpretation, except for the body image scale that remained unchanged (items 45, 46 and 47). In the hypothesised micturition scale (items 31, 32 and 33), item 33 (urinary incontinence) demonstrated poor convergent validity (0.27). It was therefore removed from this scale, leaving a two-item urinary frequency scale and a single item assessing urinary incontinence. The items in the hypothesised pain scale (items 34, 35 and 36) consistently demonstrated weak correlations with the overall scale (<0.40) in many of the subgroups studied. The pain scale was, therefore, removed leaving single items assessing abdominal pain, anal/rectal discomfort and dysuria. The original defaecation scale did not demonstrate the stable scaling properties in either stoma or non-stoma groups; it included items 38 and 39 from the main section of the QLQ-CR29 and items 52 and 53 from the stoma and non-stoma sections. Two new scales addressing the presence of blood or mucus in the stool (items 38 and 39) and the frequency of bowel movements (items 52 and 53) were therefore created. The results of the final multi-trait scaling analyses are shown in Table 3. The final module therefore has four scales and 19 single items (Fig. 1). The remaining results use these scales and items in the QLQ-CR29.

3.3. *Reliability*

3.3.1. *Internal consistency*

Cronbach's alpha coefficients for each scale are shown in Table 3. They were lowest in the blood/mucus in stool scale (0.54–0.72) and consistently higher in the body image scale (range 0.82–0.84). The Cronbach's alpha values were greater than 0.70 in 9 (75%) of the 12 groups analysed.

3.3.2. *Reproducibility*

Seventy patients returned a second HRQL assessment for the test–retest study. All scales showed good reproducibility with interclass correlations above 0.68 and single item interclass correlations were also high ($r > 0.55$).

3.3.3. *Validity*

Correlations between the scales in the QLQ-CR29 and the QLQ-C30.

All correlations between the scales in the QLQ-CR29 and the QLQ-C30 were $r < 0.40$, demonstrating that the scales in the new module did not overlap unduly with HRQL constructs in the QLQ-C30.

3.4. *Clinical validity*

3.4.1. *Known group analysis*

Mean scores in clinically distinct groups for the scales and single items of the QLQ-CR29 and the QLQ-C30 are shown in Table 4. Differences between known groups were observed in 16 of the 23 scales and items in the QLQ-CR29. In patients with and without a stoma, the differences were noted in the urinary frequency and body image scales and in the urinary incontinence, faecal incontinence, sore skin and embarrassment items. Stool frequency, abdominal pain, bloating, anxiety, dry mouth, taste, anxiety, flatulence and female sexual interest scores were different in the participants with different levels of performance. The participants receiving palliative treatment reported significantly more problems with blood/mucus in stool, hair loss, anxiety, faecal incontinence and dyspareunia than those undergoing potentially curative therapy. The QLQ-C30 demonstrated significant differences

Table 3 – Scaling results: item convergent and discriminant validity for the EORTC QLQ-CR29 scales, ($n = 310$), and for patients with and without a stoma.

	Total sample ($n = 310$)			Without a stoma ($n = 207$)			With a stoma ($n = 103$)		
QLQ-CR29 scales	Convergent	Discriminant	α	Convergent	Discriminant	α	Convergent	Discriminant	α
Urinary frequency	0.60–0.60	0.02–0.21	0.75	0.56–0.56	0.01–0.25	0.71	0.67–0.67	0.00–0.22	0.80
Blood or mucus in stools	0.53–0.53	0.00–0.25	0.69	0.57–0.57	0.01–0.38	0.72	0.37–0.37	0.00–0.34	0.54
Stool frequency	0.57–0.57	0.03–0.46	0.70	0.54–0.54	0.00–0.49	0.66	0.65–0.65	0.02–0.41	0.78
Body image	0.65–0.77	0.00–0.43	0.84	0.61–0.79	0.01–0.39	0.83	0.64–0.73	0.00–0.48	0.82

EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

Fig. 1

in all scales (except nausea and vomiting) between the participants with high or low performance scores.

3.5. *Responsiveness to change in health status over time*

Mean scores before and after palliative treatment or stoma closure are shown in Table 5. After palliative chemotherapy, a statistically significant reduction in anxiety about weight loss ($p = 0.018$) and a reduction in physical function and pain ($p = 0.045$) were reported. After closure of the temporary stoma, significant improvements in social function (QLQ-C30) were reported ($p = 0.002$), but other scores were unchanged.

4. Discussion

This study tested the EORTC QLQ-CR29 in an international sample of patients with colorectal cancer. Combined psychometric and clinical analyses led to a revision of the hypothesised scales and confirmed the single items. Further testing demonstrated that this module was reliable, not overlapping with HRQL issues in the core questionnaire and able to discriminate between known groups of patients with colorectal cancer. Debriefing information did not identify any major omissions and most participants reported that the questionnaire was easily completed within 15 min. The EORTC QLQ-

During the past week:	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NO T HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

Fig. 1 (*continued*)

CR29 is therefore recommended as a reliable and valid tool to use with the QLQ-C30 to assess HRQL in clinical trials and other research settings in patients with colorectal cancer.

Measurement of HRQL in clinical trials in colorectal cancer provides valuable information that may influence clinical decision making and may be used to inform future patients about how they will feel after treatment.[15] Health-related quality of life outcomes that are important in colorectal cancer include not only generic information (e.g. physical and social function) but also information regarding the impact of treatment on bowel, bladder and sexual function. Existing measures commonly used for this patient group include the FACT-C and the original EORTC colorectal questionnaire.[5,6] The EORTC QLQ-CR29 will add to this portfolio and it has potential benefits of being developed and tested in an international setting and it has subscales and items for stoma and non-stoma patients that provide comparable data. Translations into Danish, Dutch, French, German, Greek, Hungarian, Italian, Japanese, Korean, Norwegian, Portuguese, Brazilian, Russian, Spanish, Taiwanese and Turkish are now available.

Table 4 – Known group comparisons: mean baseline scores and standard deviation for scales and items in the QLQ-C30 and CR29 for clinically distinct groups.

	Stoma (*n* = 116)	No stoma (*n* = 235)	P value[a]	Karnofsky score < 80 (*n* = 58)	Karnofsky score > 80 (*n* = 281)	P value[a]	Palliative treatment, (Group 6, *n* = 76)	Curative treatment, (Groups 1 to 5, *n* = 275)	P value[a]
CR29 scales									
Urinary frequency	44 (28)	33 (27)	<0.001	40 (27)	36 (27)	0.330	38 (30)	37 (27)	0.900
Blood and mucus in stool	6 (15)	8 (16)	0.310	8 (19)	7 (16)	0.933	7 (20)	7 (15)	0.068
Stool frequency	21 (25)	21 (24)	0.930	26 (24)	19 (24)	0.024	18 (21)	22 (25)	0.270
Body image	26 (28)	16 (24)	<0.001	22 (25)	19 (26)	0.161	20 (27)	19 (26)	0.601
CR29 single items									
Urinary incontinence	13 (23)	7 (19)	0.002	8 (21)	9 (20)	0.645	7 (16)	9 (21)	0.418
Dysuria	7 (18)	4 (13)	0.150	5 (15)	5 (15)	0.997	4 (15)	5 (15)	0.636
Abdominal pain	20 (28)	17 (25)	0.547	27 (33)	16 (23)	0.029	18 (27)	18 (26)	0.983
Buttock pain	18 (28)	13 (25)	0.163	16 (28)	15 (26)	0.945	16 (28)	14 (26)	0.764
Bloating	17 (25)	21 (28)	0.206	31 (30)	17 (25)	<0.001	19 (28)	20 (27)	0.586
Dry mouth	28 (30)	27 (29)	0.703	36 (35)	25 (28)	0.029	31 (29)	26 (29)	0.172
Hair loss	12 (26)	11 (24)	0.867	12 (25)	11 (24)	0.700	26 (35)	7 (19)	<0.001
Taste	15 (29)	15 (27)	0.756	21 (33)	13 (25)	0.073	19 (31)	14 (27)	0.219
Anxiety	44 (34)	41 (32)	0.615	49 (34)	40 (32)	0.053	48 (32)	41 (33)	0.072
Weight	19 (28)	22 (29)	0.228	23 (31)	20 (28)	0.598	23 (31)	20 (28)	0.635
Flatulence	27 (26)	26 (30)	0.623	36 (34)	25 (27)	0.023	23 (30)	27 (29)	0.163
Faecal incontinence	18 (28)	7 (17)	<0.001	13 (26)	11 (20)	0.876	7 (16)	12 (23)	0.096
Sore skin	25 (30)	13 (23)	<0.001	18 (28)	17 (26)	0.768	14 (23)	17 (27)	0.352
Embarrassment	29 (36)	13 (24)	<0.001	21 (30)	17 (28)	0.214	16 (27)	19 (30)	0.615
Stoma care problems	15 (27)	–	–	25 (37)	12 (24)	0.134	7 (14)	16 (22)	0.407
Sexual interest (men)	81 (29)	76 (28)	0.139	83 (27)	77 (28)	0.269	79 (25)	77 (30)	0.948
Impotence	42 (44)	29 (37)	0.107	40 (42)	34 (40)	0.475	32 (37)	34 (41)	0.929
Sexual interest (women)	93 (16)	86 (23)	0.167	95 (12)	87 (23)	0.081	89 (18)	88 (23)	0.953
Dyspareunia	10 (21)	6 (18)	0.266	11 (27)	6 (16)	0.792	0 (0)	9 (21)	0.034
QLQ-C30 scales									
Physical	73 (24)	80 (22)	0.004	59 (27)	82 (19)	<0.001	77 (24)	77 (23)	0.830
Role	61 (37)	72 (31)	0.013	49 (38)	73 (30)	<0.001	70 (29)	68 (34)	0.723
Emotional	73 (26)	75 (24)	0.737	64 (28)	77 (23)	<0.001	75 (24)	74 (25)	0.989
Cognitive	82 (21)	82 (20)	0.663	71 (25)	84 (19)	<0.001	84 (20)	81 (21)	0.233
Social	63 (33)	75 (28)	0.001	58 (29)	74 (29)	<0.001	76 (28)	70 (30)	0.082
Overall quality of life	39 (25)	36 (23)	0.307	51 (24)	33 (22)	<0.001	39 (24)	36 (23)	0.377
Fatigue	40 (27)	36 (26)	0.154	53 (26)	34 (25)	<0.001	41 (26)	37 (27)	0.224
Nausea and vomiting	10 (20)	9 (16)	0.635	13 (21)	9 (17)	0.066	10 (18)	9 (18)	0.342
Pain	28 (31)	22 (26)	0.106	36 (30)	22 (26)	<0.001	24 (29)	24 (28)	0.915

Note: High score for functional scales = better function, whereas high symptom scores = more problems.
[a] Wilcoxon rank sum test.

They have also been developed in patients undergoing surgery in the curative or palliative settings as well as in patients undergoing pre-operative radiation and adjuvant chemotherapy. Permission to use the module is available from the EORTC Quality of Life Department.[16]

Although this was a large multi-centre study including over 300 patients, there are some remaining clinical validity issues that require further work. Few changes in HRQL were observed in the 3-month interval that patients received palliative chemotherapy. This may have been because the disease was stable during this time frame. Importantly the scores reported in the QLQ-C30 over the same 6 months were also similar, supporting this observation. Additionally in the small sample of patients studied before and after closure of a temporary stoma, no changes were observed in the QLQ-CR29 scores, and there was only one significant change in QLQ-C30 scores (social function, $p < 0.01$). The interpretation of this observation is difficult. It may represent a small and heterogenous sample size, or it may mean that few HRQL changes did occur. Others have noted that after stoma closure HRQL scores may improve or remain static.[17] Further work including qualitative studies is needed to understand this complex issue. It is encouraging, however, that the module was able to distinguish between known groups of patients with different performance scores and the larger group with and without a stoma.

Another area that may need further work is the assessment of sexual function after treatment for rectal cancer. The QLQ-CR29 was designed to be brief and therefore the sexual items were deliberately few. It is suggested that in trials of rectal surgery or neo-adjuvant radiotherapy, there may be a need to add a comprehensive assessment of sexual outcomes

Table 5 – Clinical validity: sensitivity to change in clinical health status before and after stoma closure and before and after palliative treatment (numbers are mean scores and standard deviations).

	Before palliative treatment, (n = 45)	After palliative treatment (n = 45)	p-Value[a]	Before stoma closure (n = 20)	After stoma closure (n = 20)	p-Value[a]
CR29 scales						
Urinary frequency	34 (30)	33 (28)	0.820	29 (25)	24 (19)	0.367
Blood and mucus in stool	5 (18)	3 (7)	0.404	3 (7)	6 (11)	0.506
Stool frequency	16 (21)	15 (21)	0.730	32 (38)	44 (26)	0.387
Body image	11 (20)	13 (21)	0.384	28 (31)	15 (18)	0.128
CR29 single items						
Urinary incontinence	5 (12)	5 (14)	1.000	5 (13)	10 (21)	0.165
Dysuria	1 (5)	1(5)	1.000	5 (18)	0 (0)	0.337
Abdominal pain	12 (19)	7 (17)	0.160	13 (29)	15 (22)	0.819
Buttock pain	7 (2)	7 (2)	1.000	21 (37)	21 (37)	1.000
Bloating	13 (21)	13 (25)	0.850	11 (16)	17 (33)	0.615
Dry mouth	22 (21)	21 (22)	0.676	26 (31)	28 (30)	0.673
Hair loss	18 (26)	29 (33)	0.062	11 (22)	6 (13)	0.504
Taste	13 (25)	17 (24)	0.442	8 (20)	0 (0)	0.190
Anxiety	38 (29)	29 (28)	0.106	33 (27)	31 (21)	0.794
Weight	17 (27)	9 (18)	0.018	23 (25)	26 (34)	0.819
Flatulence	18 (24)	16 (24)	0.536	36 (37)	41 (34)	0.700
Faecal incontinence	6 (13)	4 (14)	0.662	33 (36)	23 (25)	0.337
Sore skin	7 (16)	6 (13)	0.712	36 (35)	44 (39)	0.610
Embarrassment	10 (18)	9 (18)	0.787	33 (38)	13 (17)	0.104
Stoma care problems	13 (18)	0 (0)	0.178	24 (39)	–	–
Sexual interest (men)	80 (26)	83 (26)	0.539	80 (18)	40 (37)	0.109
Impotence	17 (27)	14 (29)	0.493	50 (43)	58 (32)	0.391
Sexual interest (women)	81 (22)	88 (17)	0.082	100 (0)	90 (25)	0.356
Dyspareunia	0 (0)	4 (12)	0.351	0 (0)	0 (0)	–
QLQ-C30 scales						
Physical	86 (16)	82 (19)	0.045	78 (17)	85 (18)	0.139
Role	81 (22)	79 (29)	0.700	57 (32)	79 (34)	0.092
Emotional	83 (18)	83 (16)	0.952	85 (14)	88 (11)	0.240
Cognitive	89 (16)	89 (14)	0.865	83 (22)	92 (16)	0.089
Social	83 (23)	80 (27)	0.435	54 (26)	82 (21)	0.002
Overall quality of life	27 (19)	29 (18)	0.657	33 (18)	25 (11)	0.127
Fatigue	32 (25)	28 (24)	0.367	32 (20)	26 (22)	0.316
Nausea and vomiting	6 (10)	6 (10)	1.000	8 (16)	9 (20)	0.776
Pain	16 (22)	8 (15)	0.045	24 (24)	18 (24)	0.478

Note: High score for functional scales = better function, whereas high symptom scores = more problems.
[a] Two-tailed student's t-test.

to understand them in detail. Another approach would be for the EORTC Quality of Life Group to develop specific sexual function subscales.

In conclusion, this study shows the psychometric and clinical validity of the EORTC QLQ-CR29 questionnaire module. It is therefore recommended that the module is used as a supplement to the EORTC QLQ-C30 in clinical trials in oncology to assess health-related quality of life.

Conflicts of interest statement

None declared.

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REFERENCES

1. Sargent DJ, Goldberg RM, Jacobson SD, MacDonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant

chemotherapy for resected colon cancer in elderly patients. *N Eng J Med* 2001;**345**:1091–7.
2. Cammà C, Giunta M, Fiorica F, Pagliaro L, Craxì A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: a meta-analysis. *JAMA* 2000;**284**(8):1008–15.
3. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76.
4. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**:570–9.
5. Sprangers MAG, te Velde A, Aaronson NK. The construction and testing of the EORTC Colorectal Cancer-specific Quality of Life Questionnaire Module (QLQ-CR38). *Eur J Cancer* 1999;**35**:238–47.
6. Ward WL, Hahn EA, Mo F, Hernandex L, Tulsky DS, Cella D. Reliability and validity of the functional assessment of cancer therapy colorectal (FACT-C) quality of life instrument. *Qual Life Res* 1999;**8**:181–95.
7. Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Holzel D. Quality of life in rectal cancer patients: a four-year prospective study. *Ann Surg* 2003;**238**:203–13.
8. Neuman HB, Schrag D, Cabral C, Weiser MR, Paty PB, Guillem JG, et al. Can differences in bowel function after surgery for rectal cancer be identified by the European Organization for Research and Treatment of Cancer Quality of Life Instrument? *Ann Surg Oncol* 2007;**14**:1727–34.
9. Gujral S, Conroy T, Fleissner C, Sezer O, King PM, Avery KNL, et al. Assessing quality of life in patients with colorectal cancer: An update of the EORTC quality of life questionnaire. *Eur J Cancer* 2007;**29**:276–81.
10. Sprangers MAG, Cull A, Bjordal K, Groenvold M, Aaronson NK. The European Organisation for Research and Treatment of Cancer approach to quality of life assessment: guidelines for developing questionnaire modules. *Qual Life Res* 1993;**2**:287–95.
11. Blazeby JM, Conroy T, Hammerlid E, et alon behalf of the European Organisation for the Research and Treatment of Cancer Gastrointestinal and Quality of Life Groups. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. *Eur J Cancer* 2003;**39**:1384–94.
12. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual, 3rd edn; 2001.
13. Fayers PM, Machin D. *Quality of life: assessment, analysis and interpretation*. Chichester, New York, Weinheim, Brisbane, Singapore, Toronto: John Wiley & Sons Ltd.; 2000. 404 pp.
14. Tabachnik BJ, Fidel LS. *Using multivariate statistics*. London: Harper & Row; 1993.
15. Blazeby JM, Avery K, Sprangers M, et al. Health-related quality of life measurement in randomized clinical trials in surgical oncology. *J Clin Oncol* 2006;**24**:3178–86.
16. EORTC Quality of Life Department, http://www.groups.eortc.be/qol.
17. Pachler J, Wille-Jørgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. *Cochrane Database Syst Rev.* 2005;**18**(2):CD004323.