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Patient-reported outcomes as predictors of survival in patients with bowel cancer: a systematic review

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Abstract

Introduction The prognostic value of patient-reported outcomes (PROs) has been determined in some cancers, but a focussed review in colorectal cancer (CRC) has not yet been conducted. We systematically reviewed PRO predictors of CRC patient survival.

Methods We searched four electronic databases (from inception to May 2018), reference lists and professional organisations to identify studies reporting pre-treatment PRO predictors of overall survival (OS) or progression-free survival (PFS) in CRC identified through univariate or multivariate models. Two reviewers independently applied inclusion criteria and extracted data on study characteristics, median and 1-year survival rates, PROs assessed and model results.

Results In 25 of 27 studies ($n = 12{,}544$), at least one PRO was significantly associated with survival. Physical functioning, fatigue, pain and appetite loss predicted OS more often than other PROs in metastatic disease (19/27 studies). One study explored PRO predictors in early-stage CRC, finding emotional well-being and mood predicted OS. In mixed-stage samples (7/27 studies), physical functioning predicted OS more often than other PROs. Few studies modelled PFS, for which few PROs had predictive value.

Conclusions Physical and psychological functioning, pain, fatigue and appetite loss had prognostic significance above and beyond clinical predictors in CRC. Routine monitoring of these PROs may allow earlier detection and amelioration of problems, which may improve quality of life and perhaps extend survival. More research is needed to determine prognostic value of PROs in early-stage CRC, and prognostic significance of changes in PRO scores.

Keywords Bowel cancer · Systematic review · Patient-reported outcomes · Survival · Predictors

Introduction

Patient-reported outcomes (PROs) are often included in cancer clinical trials. They complement traditional endpoints of tumour response and survival by providing the patients' perspective on the benefits and harms of treatments [1]. PRO is a term used to describe any outcome reported directly by patients, including disease symptoms, treatment side effects and various aspects of functioning [2]. Health-related quality of life (HRQOL) is a multidimensional PRO [3, 4], such that HRQOL questionnaires often include both symptoms and functioning to capture a full range of impacts of disease and treatment. PROs are important endpoints in clinical research given the growing international consensus among healthcare providers and researchers that treatment efficacy should be demonstrated in terms of both quantity and quality of life. During routine care, standardised assessment of PROs can improve communication between the patient and healthcare provider and be used to monitor treatment response and detect unrecognised problems [5], which potentially contributes to improved patient satisfaction and HRQOL.

Multiple reviews have consistently demonstrated the role of pre-treatment, baseline PRO assessments in predicting survival in several different cancers, independent of the extent of the disease and other clinical prognostic factors [6–8]. In a meta-analysis, Quinten et al. [9] pooled data from 7417 patients with 11 different tumour types who completed

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a cancer-specific measure of HRQOL (the EORTC QLQ-C30) before randomization. They found that at least one HRQOL domain provided prognostic information for each cancer type, although the domains with the greatest prognostic power differed by cancer type. A multidisciplinary initiative that pooled international PRO trial data to examine key HRQOL issues found further evidence that HRQOL can provide prognostic information beyond clinical measures, improve prognostic accuracy in cancer clinical trials, and yield informative factors to stratify and monitor patients for supportive interventions [7]. A rapid systematic review found a positive relationship between HRQOL data and survival duration for a range of cancer patients [6]. A further review of cancer clinical trials found, in some instances, PROs were better predictors of survival than performance status [8]. Although there is overwhelming evidence for the prognostic value of baseline PROs, these previous studies did not identify any single PRO or HRQOL domain that was consistently prognostic across cancer sites, suggesting that some PROs may provide unique prognostic information that is specific to cancer type.

Colorectal cancer (CRC), including bowel, colon and rectal cancer, is a common malignancy in the developed world, with unhealthy lifestyles and diet [10] contributing to the rising incidence. Advances in screening, early diagnosis and more effective treatments have led to improved survival rates for CRC, with around 69% surviving to 5 years [11, 12]. Those diagnosed and treated for early-stage disease have a 70–90% 5-year survival rate [11, 12]. CRC survivors experience poorer physical function and depression than the general population, and suffer from long-term symptoms such as bowel problems and cancer-related distress [13]. Patients presenting with early-stage disease are more likely to have localised tumours, amenable to surgical resection, and may not require additional adjuvant treatment. Those presenting with evidence of disease spread and more advanced cancer may require extensive surgery, leading to permanent changes in bowel function, plus adjuvant chemotherapy or radiotherapy, which come with their own range of possible side effects, and therefore may experience greater treatment-related symptom burden and negative impacts on HRQOL.

Given the potential adverse health outcomes on patients, screening for specific PRO prognostic factors to identify those individuals at high risk of poor outcomes would improve risk assessment and treatment decision making in CRC. This would assist healthcare professionals to target improvements in those identified PROs through treatment and supportive care interventions to enhance HRQOL and survival outcomes of CRC survivors.

Previous studies have assessed the relationship between pre-treatment PROs and survival in CRC, and there is emerging evidence regarding the prognostic significance of changes in HRQOL scores on survival outcomes in patients with advanced colorectal cancer [14]. However, a comprehensive review of studies assessing the role of PRO's in predicting survival in CRC has not been undertaken. Thus, we undertook a systematic review of the literature to identify which pre-treatment baseline PROs predict overall or progression-free survival in CRC. In addition, we examined whether changes in PRO scores from pre- to post-treatment had prognostic value.

Methods

Electronic searches

We searched four electronic databases: MEDLINE, EMBASE, Pubmed and Cochrane from database inception to 11 May 2018. Our search strategy comprised a comprehensive set of terms for "quality of life" or "patient-reported outcome", "colorectal cancer", "prognostic", "survival" and words denoting specific PRO domains and scale acronyms often associated with PRO assessment in CRC clinical research (e.g. QLQ-C30, QLQ-CR29, FACT-G, FACT-C).

Electronic searches were supplemented by searches of the reference lists of included studies and other relevant review papers, and a web search of FDA, NIH and NIHR. We also searched for full study citations of retrieved relevant conference abstracts.

Study selection and eligibility criteria

Papers were included if

1. Study design was prospective quantitative (i.e. phase II, III or IV clinical trial, longitudinal cohort study) or a relevant review paper;
2. Sample was adults with CRC (if study included mixed tumour samples, separate analyses for the CRC subgroup needed to be reported);
3. At least one patient-reported indicator of symptom, function or well-being, including single (e.g. pain) and multidimensional (e.g. HRQOL), measured with a validated PRO instrument;
4. Baseline PRO data in the analyses;
5. At least one multivariate analysis examining PROs and survival. A multivariate analysis was defined as any statistical test to examine the effects of one or more PROs on survival and that controlled for one or more clinical, disease-related factors;
6. Reporting hazard ratios for the 'prognostic', 'predictor', 'predictive' and 'survival' data from multivariate analyses (e.g. cox proportional hazards);
7. Published in English.

We excluded cross-sectional and qualitative studies as these study designs were not conducive to multivariate analyses; studies that included paediatric samples as CRC is not a cancer of paediatric/childhood; outcomes focused on screening, objective measures or behaviours (e.g. number of hours spent walking); personality traits or psychological assessment; and PROs assessed by proxy (e.g. health provider). No limits for year or geography were applied.

Retrieved titles and abstracts were reviewed against the eligibility criteria by one reviewer (CR). If all criteria were met, or relevance was ambiguous, papers were obtained and reviewed in full. A second reviewer (RC) screened 25% of excluded abstracts, selected at random. Where study details were lacking, we contacted authors for additional information.

Data extraction and synthesis

Study sample characteristics, design, treatment/intervention type, data collection and analysis methods, PRO instruments, univariate and multivariate results including hazard ratios, confidence intervals and *p* values, and median and 1-year survival rates for the total sample were extracted by RC and cross-checked for errors and omissions by CR. Discrepancies were discussed with MK until consensus.

Meta-analysis was not feasible given our review aims and the heterogeneity of PRO instruments and covariates used in the models. We used narrative synthesis [15] to collate and summarise the evidence in descriptive tables and figures to display the PROs that emerged as significant predictors of overall or progression-free survival in CRC populations, hazard ratios and *p* values. We characterised relative effect sizes for hazard ratios as moderate (either protective [0.51–0.75] or contributory [1.35–1.99]) and large (less than 0.50 or in excess of 2), based on ratings used by the Institute of Medicine [16].

Results

Searches yielded 3841 citations, minus duplicates, of which 113 were considered potentially relevant and 27 met eligibility criteria (Fig. 1); 12 RCTs and 15 longitudinal cohort studies of chemotherapy ($n=13$), chemoradiation ($n=1$), surgery ($n=3$) or a combination of treatment modalities ($n=5$). Five studies did not report treatment received and only three studies reported ethnicity. The 27 studies (18 multicentre) included 12,544 participants with colorectal (45%) or rectal (21%) cancer; 34% unknown. Study samples varied in disease severity: one study included only early-stage disease; seven studies included mixed disease samples; 19 studies included only metastatic patients (Table 1). Sample sizes ranged from 45 to 3734 participants (60% male) from acute, community and long-term care settings across Europe, the United States, Asia and Australia. Ages ranged from 20 to 95 (mean age range 52–80).

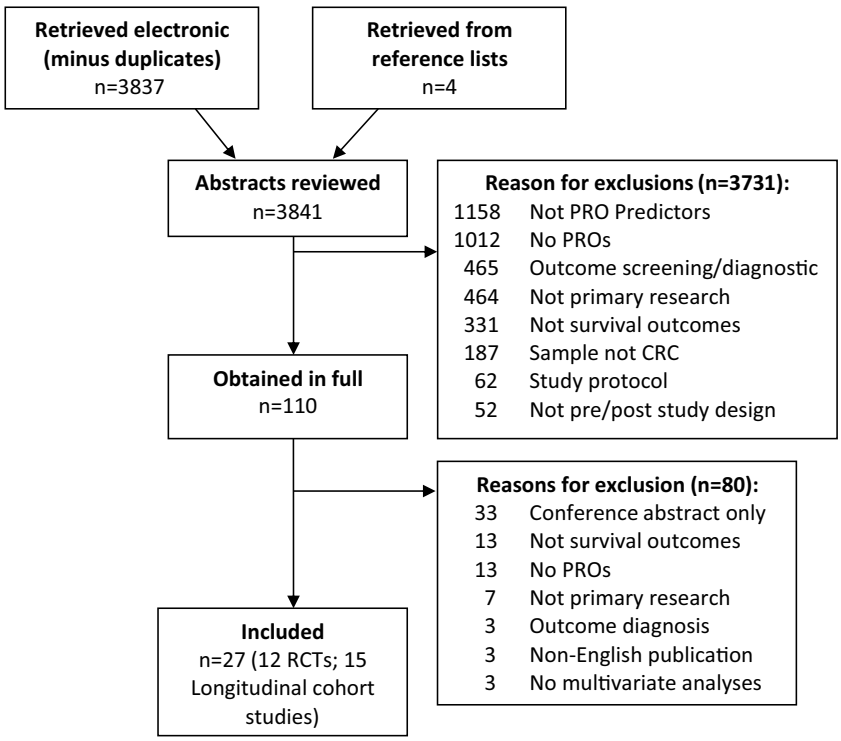

Fig. 1 Flow of studies through the screening and selection process

Table 1 Summary of study characteristics, PROs and measures, and results: overall survival

First author (year) country	Patients/*N*[a]	Covariates included in MV analysis	PROs related to OS (measure)	Univariate		Multivariate	
				HR[b] (RR)	CI	HR[b] (RR)	CI
Adams (2016) USA	517 Stage I, 454 stage II and III, 30 stage IV, 53 stage unknown; 619 colon, 349 rectum, 53 unknown; Mean age 58.2; 52% male	Age and gender, stratified by stage at diagnosis	Physical health (Veterans RAND12)	NR	–	0.25	0.19–0.34
			Metal health (Veterans RAND12)	NR	–	0.51	0.30–0.84
Aparicio (2017) France	123 metastatic CRC; mean age 80.4; 53.70% male	Treatment arm, *n* metastatic sites, primary tumour resected, Alkaline phosphatases, Leucocytes, CEA, CA 19–9, MMSE	QOL (VAS)	NS	–	NR	–
			Activity of daily living (IADL)	NS	–	0.50	0.28–0.89
Braun (2011) USA	176 Stage III, 220 stage IV CRC; mean age 53.2 (R 13–83); 53.80% male	Age, gender, stage at diagnosis and prior treatment history	Global QOL (QLQ-C30)	0.92[b]	0.87–0.98	0.93[b]	0.87–0.98
			Physical function (QLQ-C30)	NS	–	NS	–
			Role function (QLQ-C30)	NS	–	NS	–
			Emotional function (QLQ-C30)	NS	–	NS	–
			Cognitive function (QLQ-C30	NS	–	NS	–
			Social function (QLQ-C30)	0.96[b]	0.91–1.0	NS	–
			Fatigue (QLQ-C30)	NS	–	NS	–
			Nausea/vomiting (QLQ-C30)	NS	–	NS	–
			Pain (QLQ-C30)	NS	–	NS	–
			Dyspnoea (QLQ-C30)	1.06[b]	1.01–1.11	NS	–
			Insomnia (QLQ-C30)	NS	–	NS	–
			Appetite loss (QLQ-C30)	1.05[b]	1.0–1.09	1.07[b]	1.01–1.14
			Constipation (QLQ-C30)	NS	–	NS	–
			Diarrhoea (QLQ-C30)	1.07[b]	1.02–1.12	NS	–
			Financial (QLQ-C30)	NS	–	NS	–
Comella (2010) Italy	310 Metastatic; 221 colon, 89 rectum; Median age 63 (R 37–84); 60% male	A number of sociodemographic and clinical variables (not specified)	Physical function (QLQ-C30)	NR (but sig, *p* value NR)	–	0.98[b]	0.98–0.99
Diouf (2014) International (56 centres; 5 countries)	249 Metastatic; 160 colon, 86 rectum, 3 colon + rectum; Age 138 ≤ 65, 111 > 65; 61% male	Age, gender, PS, *n* sites involved, liver involvement, metastases, CT, LHD, APL, CEA	Mobility (EQ 5D)	1.9	1.33–2.71	1.66	1.12–2.48
			Self-care (EQ 5D)	NS	–	NS	–
			Usual activities (EQ 5D)	NS	–	NS	–
			Pain/discomfort (EQ 5D)	1.39	1.04–1.86	NS	–
			Anxiety/depression (EQ 5D)	1.45	1.09–1.93	NS	–
Efficace (2006) International (59 centres; 7 countries)	299 Metastatic; 148 colon, 150 rectum and rectosigmoid; median age 61.7 (R 29.4-76.1); 60.20% male	PS, *n* sites, WBC count, alkaline phosphate, liver metastases, CT, site primary tumour	Physical function (QLQ–C30)	0.99[b]	0.99–0.99	NS	–
			Emotional function (QLQ-C30)	0.99[b]	0.99–1.00	NS	–
			Social function (QLQ-C30)	0.99[b]	0.98–0.99	0.99[b]	0.99–0.99
			Fatigue (QLQ-C30)	1.01[b]	1.00–1.01	NS	–
			Nausea/Vomiting (QLQ-C30)	1.01[b]	1.00–1.02	NS	–
			Pain (QLQ-C30)	NS	–	NS	–
			Appetite loss (QLQ-C30)	1.01[b]	1.00–1.01	NS	–
			Constipation (QLQ-C30)	NS	–	NS	–
			Diarrhoea (QLQ-C30)	1.01[b]	1.00–1.01	NS	–
			Global QOL (QLQ-C30)	0.99[b]	0.98–0.99	NS	–

Table 1 (continued)

First author (year) country	Patients/*N*[a]	Covariates included in MV analysis	PROs related to OS (measure)	Univariate		Multivariate	
				HR[b] (RR)	CI	HR[b] (RR)	CI
Efficace (2008) International	443 Metastatic or recurrent; 333 colon, 106 rectum; Median age 62 (R 22–75); 59.80% male	WBC count, alkaline phosphate, *n* sites involved. Stratified by treatment and gender	Physical function (QLQ-C30)	0.93[b]	0.90–0.97	NS	–
			Emotional function (QLQ-C30)	0.95[b]	0.91–0.99	NS	–
			Social function (QLQ-C30)	0.92[b]	0.88–0.95	0.94[b]	0.88–0.96
			Fatigue (QLQ-C30)	1.10[b]	1.06–1.14	NS	–
			Nausea/vomiting (QLQ-C30)	1.13[b]	1.07–1.19	NS	–
			Pain (QLQ-C30)	1.10[b]	1.06–1.15	NS	–
			Appetite loss (QLQ-C30)	1.11[b]	1.07–1.14	NS	–
			Constipation (QLQ-C30)	NS	–	NS	–
			Diarrhoea (QLQ-C30)	NS	–	NS	–
			Global QOL (QLQ-C30)	0.91[b]	0.87–0.96	NS	–
Fournier (2016) France	90 Stage I–II, 41 stage III, 25 stage IV or unknown; 117 colon, 39 rectum; age ≥ 65; 80% male	Age, gender, tumour stage	Global health (QLQ-C30)	NS	–	NR	–
			Physical function (QLQ-C30)	0.28[b]	0.12–0.63	NS	–
			Role function (QLQ-C30)	0.28	0.13–0.59	0.32	0.13–0.83
			Emotional function (QLQ-C30)	NS	–	NR	–
			Cognitive function (QLQ-C30)	0.42	0.19–0.91	NS	–
			Social function (QLQ-C30)	0.23	0.10–0.53	NS	–
			Fatigue (QLQ-C30)	3.1	1.3–7.4	NS	–
			Nausea (QLQ-C30)	NS	–	NR	–
			Pain (QLQ-C30)	NS	–	NR	–
			Appetite loss (QLQ-C30)	NS	–	NR	–
Hernandez-Socorro (2017) Spain	75 Metastatic CRC; Mean age 65.6 (R 32–87); 79% male	Time-dependent covariates (not specified)	Global QOL: good, fair or poor (SF12)	NR	–	0.31	0.15–0.63
Hsu (2017) Canada	692 Stage II or III; 423 colon, 269 rectum; median age 67 (R 29–95); 59% male	Age, tumour classification, Lymphovascular invasion, CT	Contact with friends (PSSCAN)	NR $p=0.001$	–	NS	–
			Having people to count on for help (PSSCAN)	NS	–	NS	–
			Having people to count on for emotional support (PSSCAN)	NR $p=0.001$	–	4.36	1.97–9.64
			Desire for emotional support (PSSCAN)	NS	–	NS	–
			Fatigue (PSSCAN)	NR $p<0.0001$	–	1.99	1.34–2.95
			Health status (PSSCAN)	NR $p=0.05$	–	NS	–
			Global QOL (PSSCAN)	NR $p=0.04$	–	NS	–

Table 1 (continued)

First author (year) country	Patients/*N*[a]	Covariates included in MV analysis	PROs related to OS (measure)	Univariate		Multivariate	
				HR[b] (RR)	CI	HR[b] (RR)	CI
Innominato (2015) Europe and USA	361 Metastatic; 348 colon, 312 resected, median age 62 (R 22.3–75.9); 61.20%	Treatment arm, age, gender, site of primary tumour, disease stage, PS, *n* metastatic sites, BMI, anaemia, leucocytosis, LDH	Sleep problems (QLQ-C30)	1.39	1.11–1.74	1.36	1.07–1.72
Lis (2006) USA	8 Stage I, 16 Stage II, 51 Stage III, 77 Stage IV; mean age 52.9 (R 25–85); 56% male	Stage at diagnosis, treatment history	Health and physical (QLI)	0.94	0.91–0.97	0.94	0.91–0.98
			Social and economic (QLI)	NS	–	NS	–
			Psychological and spiritual (QLI)	NS	–	NS	–
			Family (QLI)	NS	–	NS	–
			QLI subtotal	(RR 0.95)	0.90–0.99	NS	–
Maisey (2002) UK	410 Metastatic, 91 locally advanced; 320 colon, 170 rectum; median age 62 (R 33–82); male 63%	PS, metastatic disease, tumour location, weight loss, serum albumin, haemoglobin, CEA	Physical function (QLQ-C30)	0.55	0.47–0.68	0.74	0.59–0.93
			Role function (QLQ-C30)	0.60	0.52–0.74	0.75	0.60–0.93
			Emotional function (QLQ-C30)	0.77	0.67–0.94	0.78	0.64–0.96
			Cognitive function (QLQ-C30)	0.70	0.58–0.90	NS	–
			Social function (QLQ-C30)	NR	–	0.70	0.55–0.88
			Fatigue (QLQ-C30)	1.96	1.63–2.43	NS	–
			Nausea and vomiting (QLQ-C30)	2.44	1.96–3.33	1.56	1.19–2.04
			Pain (QLQ-C30)	2.0	1.69–2.5	1.69	1.35–2.08
			Dyspnoea (QLQ-C30)	1.64	1.37–2.08	1.42	1.14–1.78
			Sleep disturbance (QLQ-C30)	1.51	1.26–1.96	1.49	1.18–1.89
			Appetite (QLQ-C30)	1.81	1.56–2.27	NS	–
			Constipation (QLQ-C30)	1.25	1.06–1.56	NS	–
			Diarrhoea (QLQ-C30)	1.32	1.10–1.67	NS	–
			Financial (QLQ-C30)	NS	–	NS	–
			Global QOL (QLQ-C30)	0.45	0.38–0.56	0.46	0.37–0.57
Mol (2016) The Netherlands	CAIRO1 sample: 803 metastatic; 478 colon, 60 rectosigmoid, 260 rectum, 4 multiple tumours; Median age 63 (R 27–84); 63% male. CAIRO2 sample: 736 metastatic; 336 colon, 202 rectum, 198 rectosigmoid; Median age 62 (R 27–83); 54.54% male	LDH, *n* metastatic sites, PS, resection primary tumour, treatment arm	CAIRO1 trial: physical function (QLQ-C30)	NR $p<0.001$	–	0.57	0.46–0.72
			CAIRO2 trial: physical function (QLQ-C30)	NR $p<0.001$	–	0.68	0.55–0.84
Mormont (2000) France	192 Metastatic; 136 colon, 56 rectum; Mean age 58 (R 20-75), 66.67% male	Previous treatment for metastasis, *n* metastatic sites, PS, Liver involvement, previous surgery for metastasis, CA 19.9, CEA; rest/activity.	Global QOL (QLQ-C30)	NR $p=0.004$[b]	–	NR $p=0.2$	–
			Physical function (QLQ-C30)	NR $p=0.0001$[b]	–	NS	–
			Fatigue (QLQ-C30)	NR $p=0.0003$[b]	–	NR $p=0.04$[b]	–
			Appetite loss (QLQ-C30)	NR $p<0.0001$[b]	–	NR $p=0.05$[b]	–
			Pain (QLQ-C30)	NR $p=0.02$[b]	–	NS	–
			Depression (HADS)	NR $p<0.0001$[b]	–	NR $p=0.05$[b]	–

Table 1 (continued)

First author (year) country	Patients/*N*[a]	Covariates included in MV analysis	PROs related to OS (measure)	Univariate		Multivariate	
				HR[b] (RR)	CI	HR[b] (RR)	CI
Park (2018) Korea	58 Stage IV; 36 colon, 13 rectum, 9 colon and rectum; Mean age 56.3 (R 32–88); 43.10% male	Presence of liver metastasis	Physical well-being (FACT-G)	NS	–	NS	–
			Social well-being (FACT-G)	NS	–	NS	–
			Emotional well-being (FACT-G)	NS	–	NS	–
			Functional well-being (FACT-G)	0.95[b]	0.91–0.99	0.95[b]	0.91–0.99
			FACT-G total score (FACT-G)	NS	–	0.98[b]	0.96–0.99
Quinten (2014) International	210 Stage I, II or III, 886 stage IV, 45 unknown; Age NR; 61% male	Age, gender, PS, stratified by distant metastasis.	Physical function (QLQ-C30)	NR	–	0.93[b]	0.96–0.99
			Role function (QLQ-C30)	NR	–	NS	–
			Emotional function (QLQ-C30)	NR	–	NS	–
			Cognitive function (QLQ-C30)	NR	–	NS	–
			Social function (QLQ-C30)	NR	–	NS	–
			Global health status (QLQ-C30)	NR	–	NS	–
			Nausea/vomiting (QLQ-C30)	NR	–	1.06[b]	1.01–1.07
			Pain (QLQ-C30)	NR	–	1.04[b]	1.01–1.07
			Dyspnoea (QLQ-C30)	NR	–	NS[b]	–
			Appetite loss (QLQ-C30)	NR	–	1.06[b]	1.03–1.09
Rees (2016) UK	232 Metastatic; Mean age 63.1; 69.80% male	Age, primary colorectal tumour nodal status, differentiation status of primary tumour, largest size of liver metastases, *n* liver metastases, presence of extrahepatic locally resectable disease, carcinoembryonic antigen levels, presence of histologically involved tumour resection margin	Global health (QLQ-C30)	0.69[b]	0.54–0.89	0.46[b]	0.33–0.63
			Physical function (QLQ-C30)	1.41[bc]	1.06–1.89	NS	–
			Role function (QLQ-C30)	NS	–	NS	–
			Emotional function (QLQ-C30)	NS	–	NS	–
			Cognitive function (QLQ-C30)	NS	–	NS	–
			Social function (QLQ-C30)	NS	–	NS	–
			Fatigue (QLQ-C30)	NS	–	NS	–
			Nausea/vomiting (QLQ-C30)	NS	–	NS	–
			Pain (QLQ-C30)	NS	–	NS	–
			Dyspnoea (QLQ-C30)	NS	–	NS	–
			Insomnia (QLQ-C30)	NS	–	NS	–
			Appetite loss (QLQ-C30)	NS	–	NS	–
			Constipation (QLQ-C30)	0.82[bc]	0.70–0.96	0.75[bc]	0.62–0.89

Table 1 (continued)

First author (year) country	Patients/*N*[a]	Covariates included in MV analysis	PROs related to OS (measure)	Univariate		Multivariate	
				HR[b] (RR)	CI	HR[b] (RR)	CI
			Diarrhoea (QLQ-C30)	NS	–	NS	–
			Financial difficulty (QLQ-C30)	NS	–	NS	–
			Eating problems (QLQ-LMC21)	NS	–	NS	–
			Activity/vigour problems (QLQ-LMC21)	NS	–	1.31[b]	1.15–1.45
			Abdominal pain (QLQ-LMC21)	NS	–	1.38[b]	1.08–1.77
			Anxiety problems (QLQ-LMC21)	NS	–	NS	–
			Nutritional issues (QLQ-LMC21)	1.51[b]	1.09–2.11	1.75[b]	1.20–2.55
			Taste problems (QLQ-LMC21)	1.30[b]	1.09–1.55	1.30[b]	1.08–1.57
			Dry mouth (QLQ-LMC21)	NS	–	NS	–
			Sore mouth/tongue (QLQ-LMC21)	NS	–	NS	–
			Tingling in fingers (QLQ-LMC21)	NS	–	NS	–
			Jaundice (QLQ-LMC21)	NS	–	NS	–
			Contact with friends (QLQ-LMC21)	NS	–	NS	–
			Talking about feelings (QLQ-LMC21)	NS	–	NS	–
			Sexual function (QLQ-LMC21)	NS	–	1.13[b]	1.04–1.23
Reyes (2017) USA	145 Stage I, 287 stage II, 567 stage III, 373 stage IV; 2576 colon; 1120 rectum; Age NR, 58% male	Age, gender, race, tumour stage, tumour site	Physical health (SF12)	0.42	0.36–0.48	Stage I and II: NS; Stage III and IV: HR 0.45	Stage I and II: NS; Stage III and IV: CI 0.35–0.59
			Mental health (SF12)	0.63	0.57–0.70	Stage I and II: HR 0.28; Stage III and IV: HR 0.74	Stage I and II: CI 0.14–0.53; Stage III and IV: CI 0.58–0.93
Rich (2005) France	80 Metastatic; 59 colon, 21 rectum; Median age 60 (R 36–76), 65% male	Cytokines, previous treatment for metastases, *n* metastatic sites, CA 19.9, PS, liver involvement, rhythm related	Global QOL (QLQ-C30)	NR $p=0.018$	–	NS	–
			Physical function (QLQ-C30)	NR $p=0.007$	–	NS	–
			Appetite loss (QLQ-C30)	NR $p<0.0001$	–	NR $p<0.001$	–
			Fatigue (QLQ-C30)	NR $p<0.0001$	–	NS	–
			Depression (HADS)	NR $p=0.002$	–	NS	–
Richardson (1990) USA	8 Stage I, 23 stage II or III, 11 stage IV; All rectal; Age (R 30 ≥ 80); 70.20% male	None	Depression (BDI)	NS	–	–	–
Schofield (2016) Australia	429 Metastatic; median age 67 (R 32–86); male 63%	Treatment arm, PS, neutrophils, alkaline phosphate, prior RT, primary tumour resected	Optimism (LOT)	NS	–	NS	–
			Hopefulness (State Hope Scale)	0.75	0.60–0.94	NS	–
			Anxiety (HADS)	NS	–	NS	–
			Depression (HADS)	2.04	1.52–2.70	1.72	1.23–2.38
			Overall HRQOL (EQ-5D)	0.56	0.45–0.71	0.73	0.57–0.94

Table 1 (continued)

First author (year) country	Patients/*N*[a]	Covariates included in MV analysis	PROs related to OS (measure)	Univariate		Multivariate	
				HR[b] (RR)	CI	HR[b] (RR)	CI
Sharma (2013) UK	97 Early-stage non-metastatic, median age 70 (R 39–86); 67% male	TNM stage	Anxiety (HADS)	NS	–	NS	–
			Depression (HADS)	NS	–	NS	–
			Positive affect (PANAS)	NR $p=0.05$	–	NS	–
			Negative affect (PANAS)	NS	–	NS	–
			Physical well-being (FACT-C)	NS	–	NS	–
			Social and family well-being (FACT-C)	NS	–	NS	–
			Emotional well-being (FACT-C)	NR $p=0.05$	–	7.0[d]	2.57–19.04
			Functional well-being (FACT-C)	NR $p=0.05$	–	NS	–
			Additional concerns (FACT-C)	NS	–	NS	–
			The mood rating scale (MOS)	NR $p=0.04$	–	0.29	0.11–0.79
Sullivan (1995) USA	218 Metastatic; 178 colon; 31 rectum; 66% over 60 year; 61% male	None	Global functional living (FLIC)	NR $p=0.0001$	–	NR	–
Ward (2014) USA	45 Metastatic; all colon; mean age 77.1 (R 54–93); 40% male	None	Activities of daily living dependence (ADL)	NS	–	NS	–
			Instrumental activities of daily living dependence (IADL)	NS	–	NS	–
			Patient-rated health status (EQ-5D VAS)	NS	–	NS	–
Wong (2014) Hong Kong	160 Stage III or IV; 90 colon, 70 rectum; mean age 62 (R 54–72); 55% male	Primary tumour site, active treatment, stoma, time since diagnosis, tumour stage	All domains (PWB; SWB; WWB; FWB; CCA) (FACT-C)	NS	–	NS	–
			Physical function (FACT-C)	0.97[b]	0.96–0.99	0.92[b]	0.85–0.99
			Role physical (FACT-C)	0.97[b]	0.96–0.99	NS	–
			Bodily pain (FACT-C)	NS	–	NS	–
			General health (SF12)	0.97[b]	0.95–0.99	0.85[b]	0.75–0.96
			Vitality (SF12)	NS	–	1.15[b]	1.03–1.29
			Social functioning (SF12)	NS	–	NS	–
			Role emotional (SF12)	NS	–	NS	–
			Mental health (SF12)	NS	–	1.13[bc]	1.01–1.27
You (2011) USA	54 Locally recurrent rectal cancer (stage NR), median age 51, 50.70% male	Treatment arm	Cancer-specific HRQOL (FACT-C total score)	NS	–	NR	–
			Pain intensity score (BPI)	1.18[b]	1.02–1.37	1.18[b]	1.02–1.37

PRO assessment

PROs were assessed with generic (SF-12 ($n=4$ studies), EQ-5D ($n=3$)), cancer-specific (FACT-G/FACT-C ($n=4$), QLQ-C30/QLQ-LMC21 ($n=13$)) or domain/construct-specific ($n=13$) PRO instruments. Despite these PRO instruments assessing multiple outcomes (i.e. multi-domain), only total scores and/or scores on selected domains were examined as predictors of survival; less than half of the studies (41%) included all domains assessed by the instruments in the univariate models. A number of covariates were included in models, mainly clinical variables such as tumour characteristics, disease stage, treatment type and blood tests (Table 1). Nine studies included age and eight studies performance status in models exploring associations between PROs and other variables.

Baseline PRO predictors of overall survival (OS)

All 27 studies assessed baseline PRO predictors of OS (Table 1). Median survival ranged from 7 months to 5.9 years; 16 studies did not report median survival. Percentage of patients alive at one year ranged from 43.5 to 93%; 22 studies did not report the percentage alive at 1 year. All studies performed analyses using Cox Proportional Hazards model except for one study that determined PRO predictors using Esteve's model adjusted for age-related mortality.

Table 1 presents summaries of key data for studies that assessed PRO predictors of OS. Reporting of the size of the PRO effect was inconsistent; some studies only reported statistical significance and eight did not report hazard ratios (Table 1). Further, in some studies, hazard ratios were calculated such that greater risk was attributed to lower PRO scores, while in others, lower risk was attributed to lower PRO scores. This is an artefact of differences in the direction of scoring of the PROs in that for some a high score is indicative of better HRQOL, while for others the opposite is the case. To provide consistent interpretation across all studies [8], in Table 1, we inverted hazard ratios and confidence intervals where higher values indicated worse functioning so that for all PRO scores, higher scores reflected better outcomes. Figures 2 and 3 indicate the number of studies that included PROs in univariate and multivariate models, and the number that found PROs were significant predictors of survival in mixed disease samples and Figs. 4 and 5 in metastatic disease samples.

Studies of CRC without evidence of spread

Only one study explored PRO predictors of survival in early-stage non-metastatic CRC patients [17]. Positive affect, emotional well-being, functional well-being and mood were significant predictors of overall survival in univariate models.

Table 1 (continued)

OS overall survival, *PRO* patient-reported outcome, *HRQOL* health-related quality of life, *NR* not reported, *NS* not statistically significant, *R* range, *HR* hazard ratio, *RR* relative risk, *CI* confidence interval, *MV* multivariate, *CEA* carcinoembryonic antigen, *MMSE* mini-mental state examination, *PS* performance status, *CT* chemotherapy, *RT* radiotherapy, *LDH* lactate dehydrogenase, *ADL* activities of daily living, *BDI* beck depression inventory, *BPI* brief pain inventory, *EQ-5D* EuroQol group 5-dimension preference-based quality-of-life measure, *FACT-C* functional assessment of cancer therapy—colorectal cancer, *FACT-G* functional assessment of cancer therapy—general, *FLIC* Functional Living Index Cancer, *HADS* Hospital Anxiety and Depression Scale, *IADL* instrumental activities of daily living, *LOT* life orientation test, *MOS* medical outcomes study, *PANAS* positive and negative affect schedule, *PSSCAN* the psychosocial screen for cancer, *QLI* Quality-of-life index, *QLQ-C30* Quality-of-Life Questionnaire Core 30, *QLQ LMC21* Quality-of-Life Questionnaire Liver Metastases Colorectal 21, *QOL* Quality of Life, *SF12* Short Form 12

[a] *N* refers to the number of study participants that completed PRO assessments

[b] Hazard of dying is smaller with good function/global QOL indicated by a HR < 1; hazard of dying is greater with high symptom indicated by a HR > 1

[c] Hazard ratio is in the unexpected direction

[d] Questionable accuracy due to excessive size of HR

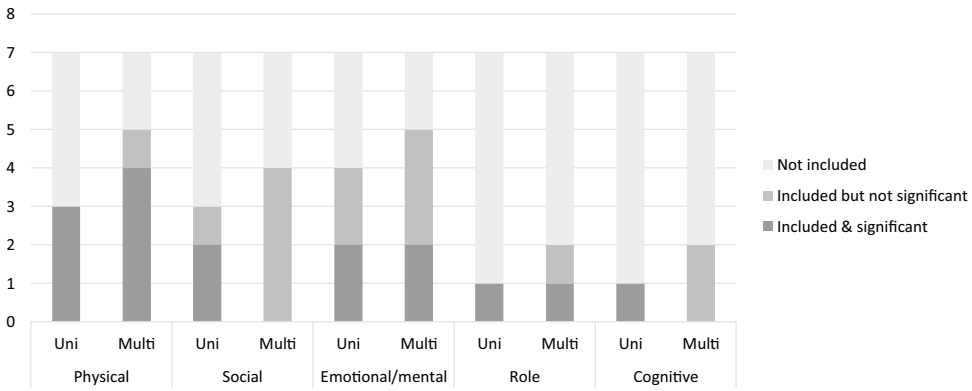

Fig. 2 The number of functioning domains assessed as predictors of overall survival in 7 studies of mixed samples in univariate and multivariate analyses

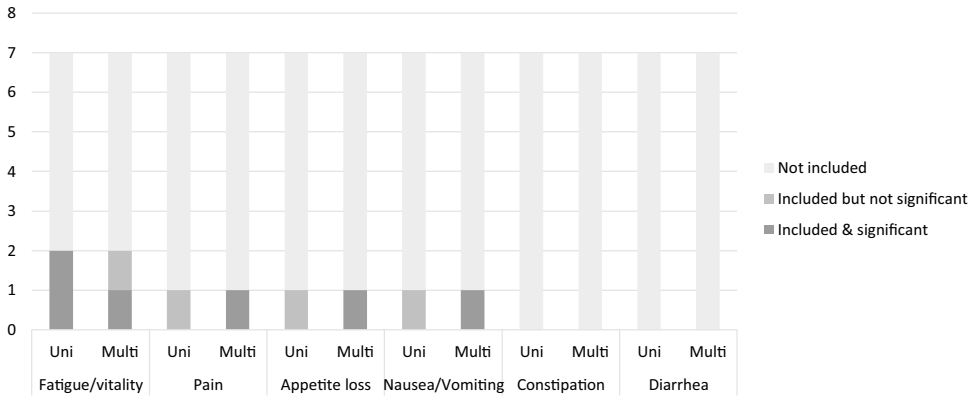

Fig. 3 The number of symptom domains assessed as predictors of overall survival in 7 studies of mixed samples in univariate and multivariate analyses

Only emotional well-being and mood remained significant predictors of OS in multivariate models.

Studies of mixed disease stage samples

Across the seven studies of mixed early- and late-stage CRC patients, five explored PROs as predictors of survival by univariate analysis (Figs. 2 and 3). Physical functioning predicted OS more often than other functioning PROs (Fig. 2). In multivariate analyses, physical functioning predicted OS more often than other PROs in mixed disease stage patients (Fig. 2). Fatigue, pain, appetite loss and nausea/vomiting were infrequently included as potential predictors of survival in mixed disease stage patients, but when included, they emerged as significant predictors of OS in both univariate and multivariate models (Fig. 3). Limitations of note for these studies include if not all PROs assessed by the PRO instruments were entered in univariate or multivariate analyses [9, 18, 19]; > 20% of study sample was excluded from baseline PRO assessment (e.g. missing data [18]); and limited information about the study sample was reported [9].

Studies of CRC with evidence of disease spread

Across the 19 studies of metastatic patients, including two studies of CRC stage III/IV, 17 explored PROs as predictors of survival by univariate analysis; two studies did not conduct univariate analysis (Figs. 4 and 5). Physical functioning predicted OS more often than other functioning PROs, followed by emotional functioning (including anxiety and depression) (Fig. 4), and a number of symptoms (fatigue, pain and appetite loss) (Fig. 5). In multivariate analyses, 17 studies found at least one PRO to be significantly associated with OS (Figs. 4 and 5). One study did not conduct multivariate analysis and only one study failed to find PROs statistically significant predictors of OS. Physical functioning predicted OS more often than other functioning PROs (Fig. 4), while pain and appetite loss predicted OS more often than other symptoms in metastatic CRC patients (Fig. 5). Limitations of note for these studies include if not all PROs assessed by the PRO instruments were entered in univariate or multivariate analyses [20–29]; > 20% of study sample was excluded from baseline PRO assessment (e.g. missing data [20, 22, 30–32]); or incomplete statistics (i.e. HR, CI, median survival not reported for PROs [27, 33]) or sample descriptors (e.g. treatment type; age at time of

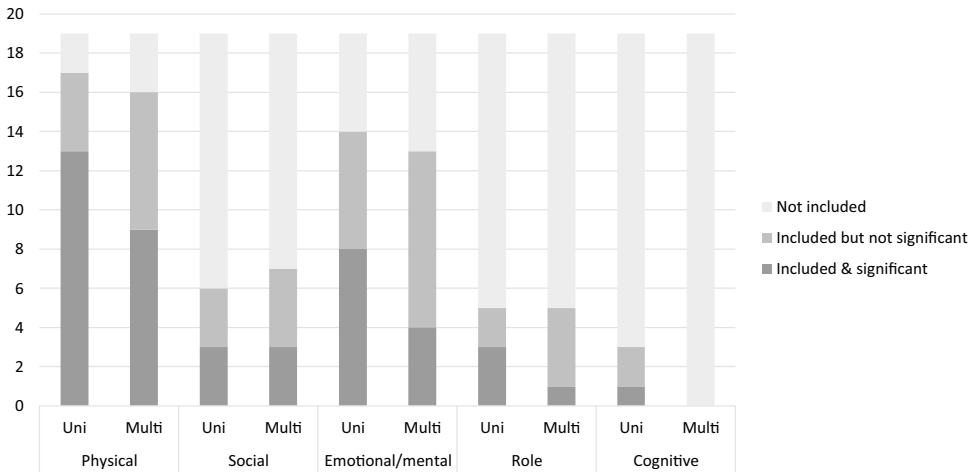

Fig. 4 The number of functioning domains assessed as predictors of overall survival in 19 studies of metastatic disease samples in univariate and multivariate analyses

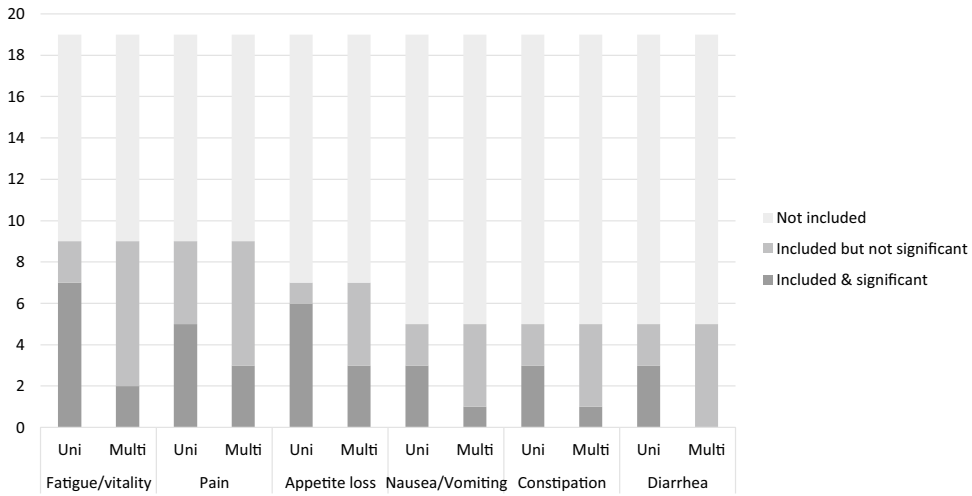

Fig. 5 The number of symptom domains assessed as predictors of overall survival in 19 studies of metastatic disease samples in univariate and multivariate analyses

diagnosis rather than at PRO completion [14, 32, 34]) were reported.

Baseline PRO predictors of progression-free survival (PFS)

Of the 27 included studies, only four assessed baseline PRO predictors of PFS (Table 2). All four were multicentre phase III trials of chemotherapy (single or combination) for a total of 1223 patients with metastatic CRC (59.5% male). None of the studies reported ethnicity. Only one study reported median survival (17.7 months, 95% CI 13.3–19.4) [20]; none reported percentage of patients alive at 1 year (Table 2). All four performed univariate and multivariate analyses using Cox Proportional Hazards model. Few PROs were entered into univariate or multivariate models (Table 2). Only higher sleep quality and overall HRQOL scores at baseline predicted PFS (Table 2). No inversions of hazard ratios and confidence intervals were required.

Post-treatment PRO predictors of survival

Only three studies analysed post-treatment PROs (e.g. PRO change scores) as predictors of survival. One study that analysed PROs in 361 metastatic patients as time-dependent covariates over a median 7-year follow-up found persistent or newly developed sleep complaints, which predicted significantly shorter OS, with a 36% estimated risk of earlier death (HR 1.37, 95% CI 1.08–1.72, $p = 0.008$) [25]. Another study found postoperative anxiety, depression (HADS), negative affect (PANAS), mood (MRS), functional well-being and additional colorectal concerns (FACT-C), which predicted long-term (i.e. > 5 years) OS on univariate analysis ($p < 0.1$) in 97 early-stage non-metastatic patients. However, only additional colorectal concerns independently predicted OS when other PROs and TNM stage were used as covariates (HR 0.36, 95% CI 0.16–0.89, $p = 0.02$) [17]. Finally, a study of 396 stage III/IV patients found a change in physical and social function from baseline to 3 months post treatment

Table 2 Summary of study characteristics, PROs and measures, and results: Progression-free survival

First author (year) country	Patients/*N*[a]	Covariates included in MV analysis	PROs related to PFS (measure)	Univariate		Multivariate	
				HR[b]	CI	HR[b]	CI
Aparicio (2017) France	123 Metastatic (83 primary); mean age 80.4; 53.7% male	Treatment arm, *n* metastatic sites, primary tumour resected, Alkaline phosphatases, Leucocytes, CEA, CA 19–9, MMSE	HRQOL (VAS)	NS	–	–	–
			ADL (IADL)	NS	–	–	–
Comella (2010) Italy	310 Metastatic; 221 colon, 89 rectum, Median age 63 (R 37-84); 60% male	A number of sociodemographic and clinical variables (not specified)	Physical functioning (QLQ-C30)	NS	–	–	–
Innominato (2015) Europe and USA	361 Metastatic; 348 colon, 312 resected; Median age 62 (R 22.3–75.9); 61.20%	Treatment arm, age, gender, site of primary tumour, disease stage, PS, *n* metastatic sites, BMI, anaemia, leukocytosis, LDH	Sleep quality (QLQ-C30)	1.44	1.16–1.78	NR	–
Schofield (2016) Australia	429 Primary metastatic; median age 67 (R 32–86); 63% male	Treatment arm, PS, neutrophils, alkaline phosphate, prior RT, primary tumour resected	Optimism (LOT)	NS	–	NS	–
			Hopefulness (State Hope Scale)	NS	–	NS	–
			Anxiety (HADS)	NS	–	NS	–
			Depression (HADS)	NS	–	NS	–
			Overall HRQOL (EQ-5D)	0.76	0.62–0.93	NS	–

PFS progression-free survival, *MV* multivariate, *PRO* patient-reported outcome, *HRQOL* health-related quality of life, *ADL* activities of daily living, *VAS* visual analogue scale, *IADL* instrumental activity of daily living scale, *QLQ-C30* Quality-of-life questionnaire—core 30, *LOT* life orientation test, *HADS* Hospital Anxiety and Depression Scale, *EQ-5D* EuroQol group 5-dimension preference-based quality of life measure, *NR* not reported, *NS* not statistically significant, *R* range, *HR* hazard ratio, *CI* confidence interval

[a]*N* refers to the number of study participants that completed PRO assessments

[b]Hazard of dying is smaller with good function/global QOL indicated by a HR < 1; hazard of dying is greater with high symptom indicated by a HR > 1

significantly, which predicted OS in multivariate analysis; a lower risk of death was associated with a 10-point improvement in physical function (HR 0.86, 95% CI 0.78–0.94, $p = 0.001$), while a higher risk of death was associated with a 10-point improvement in social function (HR 1.08, 95% 1.02–1.13, $p = 0.008$) [14]. No studies investigated whether post-treatment PROs predicted PFS. Limitations of note for these studies include if not all PROs assessed by the PRO instruments were entered in the univariate or multivariate analyses [20, 21, 25] and in one study > 20% of the study sample was missing from baseline PRO assessment [20].

PRO predictors of OS according to regression models

Three studies conducted in the UK performed stepwise regression analyses to determine PRO predictors of OS [35–37]; two including patients with colorectal liver metastases and one in rectal cancer patients. A study of 43 colorectal liver metastases patients that included clinical and PRO covariates in the survival analysis did not find HRQOL (Rotterdam Symptom Checklist; RSC), anxiety and depression (HADs) and health status (Sickness Impact Profile; SIP) to be significant predictors of OS at $p < 0.001$; however, health status and depression emerged as significant independent predictors of survival at $p < 0.05$ [36]. In another sample of 50 colorectal liver metastases patients, low baseline physical symptom score (RSC) was a stronger predictor of survival than tumour size measured by CT scan [35]. A weak negative correlation was found between survival and baseline anxiety and depression but not statistically significant. The best model for predicting survival included several PROs: diarrhoea (RSC), eating (SIP), restlessness (HADS), ability to work (SIP) and sleep (SIP). Baseline physical (RSC), anxiety, depression (HADS) and health status (SIP) scores were significantly positively correlated with tumour growth at 5-month CT scans. In 65 rectal cancer patients, preoperative physical function, nausea/vomiting and sexual function (QLQ-C30), together with age predicted postoperative 1-year survival with 76.8% accuracy [37]. Preoperative physical function (QLQ-C30; SF36), social function, mental health and energy/vitality (SF36) were positively correlated

with survival, whereas preoperative fatigue and dyspnoea (QLQ-C30) were negatively correlated with survival.

Discussion

We reviewed studies that investigated baseline PRO predictors of CRC patient survival based on univariate or multivariate analyses in prospective studies. A mix of generic, disease-specific and single-domain PRO instruments was used. Although this had the potential for a comprehensive suite of PROs to be considered as predictors of survival, many studies only included total scores or selected certain domains for inclusion in the survival analyses. While a few studies explicitly stated the selected domains they aimed to consider as predictors of survival, many did not and only entered and/or reported on selected domains without providing a rational or justification for doing so. Notably, no study used the EORTC QLQ-C29 colorectal cancer-specific module, and only one study used the colorectal liver metastasis-specific module, the QLQ-LMC21, despite more than half the included studies including only metastatic patients. This is a missed opportunity to assess a number of PROs relevant in metastatic disease, and highlight the need for appropriate PRO instrument selection relevant to the study questions, population and context.

Physical functioning consistently emerged as a predictor of OS more often than other PROs in mixed disease stage samples as well as patients with metastatic disease in both univariate and multivariate models. Emotional functioning, social functioning and global HRQOL/health status were also commonly included in models but less consistently emerged as significant predictors of OS. The finding that global HRQOL is predictive of survival is clinically unhelpful as it is unclear which aspect of HRQOL should be addressed to improve patient outcomes. Symptoms were less frequently included in models but appetite loss, pain and fatigue were the most common significant predictors of OS. It is difficult to comment on the magnitude of the associations as some hazard ratios were based on one unit increase on a continuous PRO scale (usually providing hazard ratios closer to 1), while others used dichotomised PRO scales based on median values (i.e. lower versus higher scores). In Table 1, the latter have large hazard ratios while the former have very small yet statistically significant hazard ratios. This makes them incomparable. Of note, 10 studies did not report hazard ratios for univariate analyses compared to three studies that did not report hazard ratios for multivariate analyses, further preventing comparability across studies. Overall across studies, most associations between PROs and survival were in the expected direction, i.e. better PROs predicted better survival, with one notable exception that reported higher risk of death associated with a 10-point improvement in social function [14]. This finding seems counter-intuitive. A possible explanation for this finding may be due to a coding error in the direction of the scale, an error in reporting or possibly due to vagaries of sample variation.

Few studies investigated whether baseline PROs predicted PFS, and these assessed a small number of different PROs in univariate or multivariate models. Only higher sleep quality and global HRQOL scores significantly predicted PFS. All four studies that assessed PRO predictors of PFS were homogeneous samples (i.e. metastatic CRC patients receiving chemotherapy), and results may not be generalisable to other CRC disease stages.

Our findings support the link between PROs and survival in CRC, consistent with others [6–8]. However, many PROs that were significant predictors of survival in univariate analyses were no longer significant in multivariate analyses. As PROs are often correlated, this finding may in part be a methodological artefact, as illustrated for the EORTC QLQ-C30 by Van Steen et al. [38]. They found that correlations among PROs included as predictor variables in survival analysis (termed multicollinearity) lead to model instability, such that the PROs that remain significant in multivariate models might depend on the method used to build the multivariable model. They also recommended that the global HRQOL scale of the QLQ-C30 should be excluded from prognostic factor analysis due to its high correlations with other variables in the QLQ-C30 instrument. Only five studies in our review considered multicollinearity in their analyses. Of these, four had used the QLQ-C30 but only one excluded global HRQOL from the models. Of note, 12 of 27 studies assessed PROs with the EORTC QLQ-C30 but only four considered multicollinearity in their analyses. As explained by Van Steen et al. [38], neither of two correlated factors may be identified as statistically significant in multivariate analyses even though both have an influence on survival. Consequently, the evidence we collated about univariate predictors may tell a more reliable story about which PROs are associated with survival than the evidence from multivariate analyses. Future studies of PRO inclusion in prognostic factor analyses should consider use of the Cox proportional hazards model using the Ridge regression (Cox-R) to estimate hazard ratios, as this was found to be the best approach when performing prognostic factor analyses with multiple and collinear PRO scales, particularly in situations of high multicollinearity, small sample sizes and low event rates [39]. Other alternative approaches may include testing for the association between PROs above and beyond clinical variables as a group by using nested likelihood tests (i.e. test the improvement in model fit when adding PROs to a model that already contains clinical variables); and relatedly, move away from interpreting measures of association for individual effects and instead ask what improvement in predictive accuracy one obtains.

Our finding that several PROs predict survival in metastatic disease is important given that treatment in advanced disease is generally palliative and aimed at optimising HRQOL. Patients with more advanced CRC may present with symptoms and poorer functioning at baseline. Physical function predicted OS more often than other PROs in patients with metastatic disease, suggesting that poorer patient-reported physical functioning may represent a sensitive marker for disease progression in late-stage disease. However, these studies of late-stage disease have limited generalizability to early-stage CRC. Further, we identified only one study of early-stage CRC. Consequently, this evidence base did not allow us to determine if the prognostic value of PROs differs with disease stage.

Factors such as disease stage, treatment-related toxicities and comorbidities can impact on PROs and survival. However, few studies adjusted for age (33%), performance status (30%) or BMI (7%) in survival models, and no study adjusted for comorbidity. This is surprising given that patient age [40], BMI [41] and comorbidity have been found to predict survival in CRC patients [40–42]. A recent population-based cohort study found approximately one-third of CRC patients had at least one comorbidity, the most common being diabetes and cardiovascular disease [42]. CRC patients with comorbidities received curative intent treatment less frequently and experienced worse outcomes than patients with no comorbidity [42].

Our review highlighted several gaps in the evidence base about the prognostic value of PROs in CRC. Only one study included early-stage CRC patients and only three studies analysed post-treatment PROs as predictors of OS. Those that did found sleep complaints and physical function in metastatic patients and colorectal concerns in non-metastatic patients independently predicted > 5-year survival. Despite our inability to comment on the magnitude of the associations, we do feel that these findings have implications for patient care, treatment planning and possible risk stratification. Specifically, these findings highlight the need for routine monitoring of PROs in CRC survivors. An individual's PROs reflect how the disease and subsequent treatment are affecting them, directing the clinical team to areas of concern for the patient, and the acceptability of additional active treatment. Early detection via routine monitoring for deterioration in these PROs would enable early appropriate supportive care interventions that may improve HRQOL and possibly survival outcomes in CRC survivors. Prospective screening and intervention studies are required to test this. No studies assessed post-treatment PRO predictors of PFS. Assessment of a comprehensive suite of PROs as predictors of PFS is needed. Given the high rate of persistent side effects of treatment, high recurrence rates and the fact that some PROs are predictors of survival, PROs associated with post-treatment survival in CRC patients deserve further research. Further, PROs might be considered for stratification purposes in future clinical trials as suggested in a number of studies that have identified the value of using PROs to stratify cancer patients for treatment and to guide supportive care resources [8].

Not limiting our study inclusion to RCTs as others have done allowed us to include additional relevant and informative analyses from observational studies. Although RCTs provide the best design for assessing treatment effectiveness, RCT participants often have strict eligibility criteria and may not be representative of real-world contexts. In general, the quality of the included studies was high, based on appropriate design, conduct and being adequately powered. However, some notable limitations were observed. Not all PROs assessed by the PRO instruments used were entered in univariate or multivariate analyses; some studies had more than 20% of the study sample missing from baseline PRO assessment; or incomplete statistics or sample descriptors were reported. Heterogeneity in the PRO instruments used and which PROs and covariates were included as possible predictors in univariate and multivariate models complicates cross-study comparisons. Finally, future research should take into account the high correlations between some PROs entered simultaneously into multivariate models.

Given these limitations in the available evidence base, the multivariate analyses conducted provide a fairly conservative test of the role of PROs in predicting survival in CRC. The univariate analyses are informative for clinical decision making, and may be more reliable (as noted above). Those individual PRO predictors provide clinicians with useful insights into which symptoms and aspects of functioning might be contributing factors to improving HRQOL and survival outcomes in CRC.

Conclusions

Physical functioning and symptoms of pain, fatigue and appetite loss are prognostic of survival in metastatic and mixed disease CRC samples, above and beyond clinical predictors. These findings have possible implications for patient care, treatment planning, and risk stratification for treatment and to guide supportive care resources. Routine monitoring of PROs would allow earlier detection and amelioration of problems that could improve HRQOL outcomes and perhaps survival in CRC survivors. More work is needed on PRO predictors of survival in early-stage CRC, progression-free survival and prognostic significance of changes in PRO scores over time.

Author contributions CR conception of the study and led the design, analysis plan, data interpretation and manuscript writing. RC conducted

the data extraction and contributed to results interpretation and writing of the manuscript. KW contributed to study conception, design considerations, results interpretation and revision of the manuscript. MK contributed to study conception, study design, resolved data extraction queries, data interpretation and revision of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and Informed consent Ethics approval and consent to participate was not required for this secondary analysis.

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