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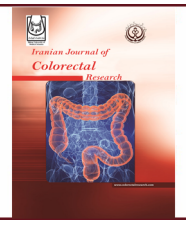

Prevalence of Long-term Patient-reported Consequences of Treatment for Colorectal Cancer: A Systematic Review

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Abstract

Context: Colorectal cancer (CRC) survivors experience persistent late effects of treatment, including a range of symptoms and functional impairments. There is limited evidence on the prevalence of such problems in CRC survivors. We conducted a systematic review to synthesize the evidence on the range and prevalence of patient-reported symptoms and functional impairments experienced by CRC survivors in the acute and long-term period following primary treatment for CRC.
Evidence Acquisition: We searched the Embase, Pubmed, and Cochrane electronic databases (from 2000 to April 2021) to identify studies reporting longitudinal prevalence (i.e., a minimum of two assessment time-points) of any patient-reported outcomes (PROs) at 12 months or more since treatment. Two reviewers independently screened and extracted data on study characteristics and PRO prevalence. PROs were synthesized descriptively across different time points (baseline, during treatment, and up to three years post-treatment) to determine the prevalence of PROs over time and the extent of persistent problems in long-term post-treatment survivorship.
Results: Of 5587 studies screened, 29 met eligibility criteria and were included. Three years after primary treatment, up to 55-65% of CRC survivors reported issues with mobility, 40% reported pain and discomfort, and up to 83% reported fecal incontinence. Many patients had impaired sexual and/or urinary function.
Conclusion: CRC survivors should be screened for persistent late effects of treatment, assessed with validated patient-reported measures. Appropriate management strategies should be implemented to reduce symptom burden and improve the quality of life of these patients.

Keywords: Bowel cancer, Systematic review, Treatment effects, Patient-reported outcomes, Survivorship

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Context

Colorectal cancer (CRC) is the second most commonly occurring cancer in men and women, accounting for approximately 10% of all cancers diagnosed annually worldwide (1). Risk factors such as obesity, unhealthy lifestyle, and diet in developed countries increase CRC risk (2). Advances in screening, diagnosis, and treatment have improved CRC survival rates, where the overall five-year survival rate is 64% and as high as 90% for early-stage CRC (3).

Despite improvements in survival, CRC survivors can experience a range of treatment effects depending on the treatment type (4-7). For patients with stage 1 to 3 CRC, unless contraindicated, surgery is the mainstay treatment. This involves removing a bowel segment, and, ideally, a restorative procedure when restoring gastrointestinal continuity is feasible. However, surgery can involve a permanent change in bowel structure, causing long-term impairment in bowel functioning such as fecal leakage, constipation, and dependence on a stoma bag (8). The potential need for a stoma is commonly considered an adverse health outcome. However, studies comparing quality of life following restorative and non-restorative procedures have not demonstrated a significant difference in patient outcomes between the two (7, 9). The addition of chemoradiation as neoadjuvant therapy or chemotherapy as adjuvant in turn depends on pre- or post-operative staging, and while these modalities have definite oncological roles, they can exacerbate functional problems, increase symptom burden, and worsen quality of life (7). Neuropathy is a common side effect of chemotherapy, which can remain present years after completing treatment (10). Radiation therapy can instigate or aggravate loose stools, bleeding, and bladder changes (4, 11).

It is commonly believed that once definitive cancer treatment is completed, survivors only require ongoing surveillance for cancer recurrence. However, research suggests that survivors continue to experience long-term physical, psychosocial, and sexual function impairments (7, 12, 13); problems that clinicians anecdotally consider resolved by 12-months post-treatment (14). Many of these problems remain unmanaged, and about half of cancer survivors experience unmet needs such as sexual dysfunction, fatigue, pain, and impaired sleep and bowel control (7, 13, 15).

Symptoms and functional impairments are best assessed through patient-reported outcomes (PROs); that is, reports that come directly from the patient about the status of their health condition without interpretation by another (16). Given the negative impact of persistent symptoms and functional impairments on survivors' quality of life, PROs are important to assess in both clinical practice and research. In clinical practice, evaluating PROs can improve care by monitoring and managing outcomes important to patients and facilitating shared-decision making (17). PROs can be useful endpoints for comparative effectiveness research and can act as predictors of survival (18, 19). Traditionally, surgeons and oncologists involved in the care of CRC survivors focus particularly on oncological outcomes and less on PROs. While some symptoms improve with time, survivors with residual symptoms at 12 months after treatment are likely to experience persistent physical, psychosocial, and sexual function impairments (7, 12, 13). Under-recognition of functional impairment may result in under-reporting, and this is likely to worsen over time. Thus, many of these problems remain unmanaged and about half of CRC survivors experience unmet needs (7, 13, 15).

While the acute effects of treatment in CRC are well recognized, the long-term prevalence of adverse treatments effects has received less attention. We need a more comprehensive understanding of the side-effects and functioning impairments that persist or develop long after treatment completion to better prepare survivors for the late effects of treatment and inform appropriate survivorship care plans. Longer-term impacts of treatment receive less attention over time as contact with specialist services becomes less frequent. Further, clinicians may tend to focus on assessment for recurrent disease, despite CRC survivors continuing to face challenges with ongoing effects of treatment (20). Problems such as sexual dysfunction, anxiety, and gastrointestinal issues are often under-recognized by health professionals and under-reported by CRC survivors (21).

Objective

We aimed to identify and summarize the range and prevalence of patient-reported symptoms and functional impairments experienced by CRC survivors in the acute and long-term period following their primary treatment for CRC and to provide information about these PRO trajectories and problems that develop or persist beyond the first year. To our knowledge, this is the first systematic review of this kind.

Data Sources

Our systematic review was conducted as per a predeveloped study protocol that outlined the research questions, search strategy, eligibility criteria, and quality assessment methods. The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (22).

Electronic Searches

The EMBASE, PubMed, and Cochrane databases were searched for records published from 2000 to 14 April 2021. Searches were limited to the publication year 2000 to account for the progression/evolution of surgical techniques in the past couple of decades.

Our search strategy comprised a comprehensive set of terms for "quality of life" or "patient-reported outcome" or "colorectal cancer", words denoting specific symptoms or functional outcomes (e.g., physical function, diarrhea, or neuropathy), and PRO measure acronyms for measures commonly used to assess PROs in CRC clinical research (e.g., QLQ-C30, QLQ-CR29, FACT-G, FACT-C). The search strategy is available in Supplement 1. Electronic searches were supplemented with hand-searching reference lists of included studies and relevant systematic reviews (e.g., reviews synthesizing evidence on treatment for NMIBC) and by the first author's name of the included studies.

Evidence Acquisition

Studies were included if:

- The sample included survivors diagnosed and treated for any stage CRC (including bowel and rectal). In the case of mixed tumor samples, >80% of the sample had to be CRC or PRO results had to be reported separately for the CRC sample AND
- They were single-arm prospective cohort or randomized controlled trial studies (these designs were selected as they would enable PRO trajectories over time) AND
- The study design included a pre/post-treatment PRO assessment or longitudinal data collection (i.e., at least two assessment time-points) for any PRO (e.g., symptoms, functioning, quality of life) and included a minimum of 12 months post-primary treatment (e.g., surgery) for CRC follow-up AND
- The prevalence or incidence of PROs (e.g., percentage of sample reporting the symptom) was reported.

We did not limit inclusion to any specific treatment or intervention type and included both single and multi-arm studies (i.e., with or without a comparison group).

Studies were excluded if:

- The sample included only pediatric or mixed cancers, and PRO results were not reported by cancer type;
- The study design was qualitative or cross-sectional;
- Outcomes were assessed by a healthcare provider or proxy (i.e., not patient-reported);
- PRO data from mixed cancer samples were combined for analysis (i.e., not reported PRO separately for CRC);
- Published in a language other than English;
- Reported only mean scores for the PROs; or
- Only a conference abstract was published.

Retrieved titles and abstracts were reviewed against the eligibility criteria by two reviewers. If all criteria were met or relevance was ambiguous, papers were obtained and reviewed in full. A third reviewer screened 25% of the excluded abstracts, which were selected at random. As 100% agreement was achieved, no further excluded abstracts were screened. One reviewer assessed full texts, and inclusion was confirmed independently by a second reviewer.

Data Extraction

Two authors independently extracted data from full texts, including study sample characteristics, design, treatment/intervention type, PROs assessed, PRO measures and assessment time-points, and PRO prevalence results (at each assessment time-point) using a standardized data extraction template. Any discrepancies in extractions against the original source were settled through discussion between reviewers and were corrected in the data extraction sheet. Where study details were lacking, authors were contacted for additional information.

Longitudinal data on the prevalence of PROs were synthesized descriptively to provide a range of prevalence for each PRO assessed at different time points from the baseline (before treatment), end of treatment, and up to five years post-treatment. Prevalence values indicate the percentage of the study sample that reported experiencing the symptom or functional problem at each assessment time-point.

Quality Assessment

Longitudinal cohort studies were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (23), and randomized controlled trials were assessed using the Consolidated Standards of Reporting Trials (CONSORT) checklist (24). Study quality was evaluated by two reviewers independently, and discrepancies were discussed until consensus was reached. Total quality scores were calculated as a percentage of the total possible score to achieve standardization across longitudinal cohort studies and randomized controlled trials.

Results

Of 5587 studies retrieved, 29 met the eligibility criteria, including 14 randomized controlled trials and 15 observational studies of rectal cancer (n=20), colon cancer (n=3), and both (n=6). The search results are presented in Figure 1. Across the included studies, more than 9111 participants completed PRO measures at baseline. The study samples varied in disease severity. Table 1 summarizes the sample characteristics, study design, and PROs collected in each of the included studies.

Quality Assessment

Cohort study quality scores (n=15) ranged from 57-90% on the STROBE checklist (Figure 2). Background, setting, and statistical methods were adequately reported across studies, while details about the handling of missing data, loss of follow-up,

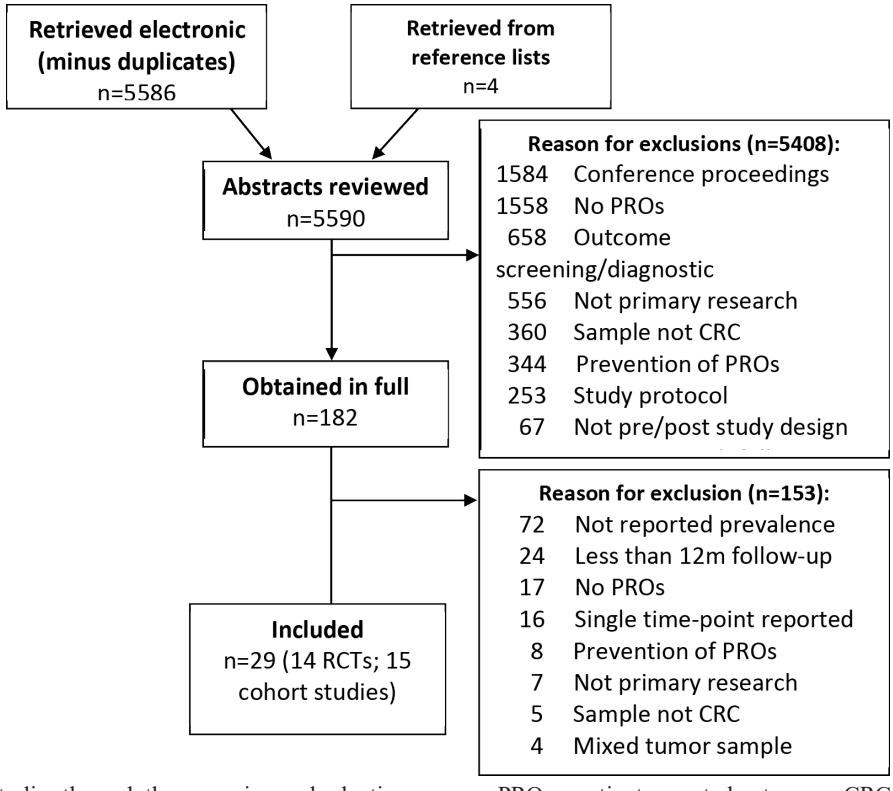

Figure 1: Flow of studies through the screening and selection process. PROs – patient-reported outcomes; CRC – colorectal cancer; RCTs – randomized clinical trials.

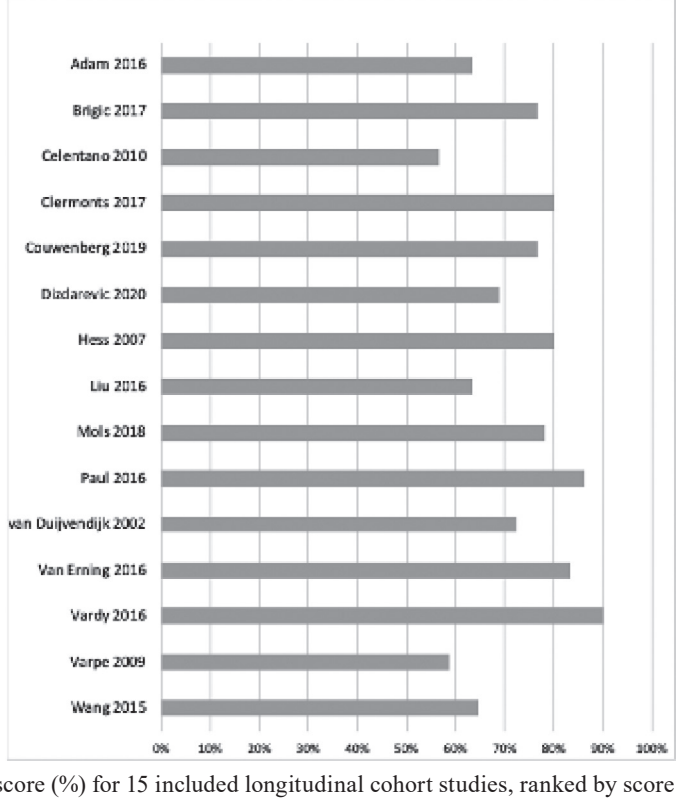

Figure 2: Quality assessment score (%) for 15 included longitudinal cohort studies, ranked by score (not including N/A).

and generalizability of results were poorly reported (Figure 3). For randomized controlled trials (n=14), the quality scores ranged from 43-73% (Figure 4). Study objectives, trial design, results, and conclusions were adequately reported, while the description of randomization methods and minimizing harms were poorly reported (Figure 5).

Patient-reported Outcomes (PROs) Assessed

Across the 29 studies, the following PROs were assessed: bowel function (n=15 studies), sexual function (n=8), urinary function (n=6), physical function (n=5), pain/discomfort (n=5), depression and anxiety (n=5), neuropathic symptoms (n=2), fatigue (n=2), and return to work (n=1).

Table 1: Characteristics of 29 included studies.

First author (year), country	CRC sample characteristics: sample size (male:female); age mean or median (age range); tumor type; disease stage; treatment; n permanent ostomy)[a]	Comparison/control group characteristics (sample size; male:female; age; tumor type, disease stage; treatment; n permanent ostomy)[a]	Study design and PRO assessment schedule	PRO (PROM)[b]
Adam (2016), France (39)	169 (111:58); Me=61 (31-80); mid and low rectal cancer; 24 T1/2, 145 T3/4, 58 N0, 111 N1-2; LAP+TME; 121	NA	Single-center prospective, longitudinal study at T0: pre-Tx; T1: 4-6w post-radiotherapy, T2: 3m; T3: 6m; T4: 12m post-Tx	Urinary function (IPSS) Sexual function (IIEF-5 and FSI)
Anderson (2013), Belgium, Canada, Denmark, Germany, Netherlands, South Korea, Spain, Sweden (45)	260 (162:98); M=67.4; rectal cancer; 18 stage I, 93 stage II, 135 stage III, 9 stage IV, 5 unknown; LAP (+TME, APR and radiotherapy for some); NR	125; 77:48; M=66.6; rectal cancer; 4 stage I, 42 stage II, 72 stage III, 3 stage IV, 4 unknown; open resection (+TME, APR and radiotherapy for some); NR	Multicenter RCT at T0: pre-Tx; T1:4w; T2:6m; T3:12m	Physical function (EQ-5D) Mental health (EQ-5D)
Biondo (2013), Spain (25)	54 (15:39); M=64.6; rectal cancer; 24 stage I, 15 stage II, 15 stage III-IV; colon J-pouch; 0	52; 12:40; M=63.6; Rectal cancer; 29 stage I, 14 stage II, 9 stage III-IV; transverse colostomy; 0	Multicenter RCT at T0: 6m; T1:36m	Bowel function (study-specific)
Brew-Graves (2021), UK (46)	46 (31:15); ≥61 years=32, <60=14; colorectal cancer with lung metastasis; 2 T1, 7 T2, 37 T3+; resection with prospect of cure+pulmonary metastasectomy; NR	46 (31:15); ≥61 years=33, <60=14; colorectal cancer with lung metastasis; 2 T1, 8 T2, 37 T3+; resection with prospect of cure; NR	Multicenter RCT at T0: pre-Tx; T1:3m; T2:6m; T3:12m; T4: 24m	Mobility, self-care, usual activity, pain and discomfort, anxiety and depression (EQ-5D-3L)
Brigic (2017), UK (26)	91 (43:47); M=71.2; colon cancer; 4 benign, 20 stage I, 32 stage II, 31 stage III; LAP, converted or open; 0	85; 34:51; M-58.2; healthy controls 85; 49:36; M=69.0; 16 stage I, 35 stage II, 34 stage III; LAP, converted or open; 0	Single-center, case-control study at T0: pre-Tx, T1: 6m; T2: 12m	Number of bowel movements per 24 hours (MSKCC BFI)
Brown (2014)[a], UK (47)	215 (135:80); Me=73 (31-94); 88 colon and 127 rectal cancer; 0 T0, 16 T1, 48 T2, 108 T3, 17 T4, 26 unknown; curative surgery (LAP or open); 91	399 (no complications group); 201:198; Me=70 (25-94); 218 colon and 181 rectal cancer; 1 T0, 20 T1, 48 T2, 235 T3, 48 T4, 47 unknown; curative surgery (LAP or open); 116	Multicenter RCT at T0 pre-Tx; T1: 2 w; T2: 3m; T3: 6m; T4: 18m; T5: 36m	Physical function (EQ-5D) Mental health (EQ-5D)
Celentano (2010), Italy (40)	20 (20:0); M=60.9; rectal cancer; 4 T1, 3 T2, 13 T3, 16 N0, 2 N1, 2 N2; autonomic nerve preserving TME; 0	NA	Single-center prospective, longitudinal study at T0: pre-Tx; T1: 3m; T2: 6m; T3: 12m; T4: 18m; T5: 24m	Urinary function (NR) Sexual function (IIEF)
Couwenberg (2019), Netherlands (28)	78 (55:23); Me=65 (40-83); rectal cancer; 28 T2, 50 T3, 45 LAR, 7 Hartmann, 26 APR; 33	78; 54:24; Me=66 (47-83); rectal cancer; 3 T2, 75 T3; 45 LAR, 2 Hartmann, 31 APR; 31	Single-center prospective, longitudinal study at T0: pre-chemo, T1: 3m, T2: 6m; T3: 12m; T4: 18m, T5: 24m	Fatigue, insomnia, pain, bowel function, urinary function, sexual function (male patients only) (QLQ-C30/ CR29)
Clermonts (2017), Netherlands (27)	44 (21:21); Me=68.5 (39-94); rectal cancer; 26 benign, 5 stage 0, 11 stage I; TAMIS; 0	NA	Single-center prospective, longitudinal study at T0: pre-Tx; T1: 12m; T2: 36m	Fecal incontinence (FISI)
Dizdarevic (2020), Denmark (29)	40 (32:8); Me=68 (61-77); distal rectal cancer, 16 T2N0, 7 T2N1, 7 T3N0, 10 T3N1; neoadjuvant chemoradiation therapy (CRT); NR	NA	Single-center prospective observational trial at T0: pre-CRT, T1: 6m, T2: 12m	Gastrointestinal and urinary symptoms, anorectal function, sexual function, overall QoL (QLQ-CR29)

Fazio (2007), US, France, Germany, Australia (30)	178 (94:50); M=60.15; Low rectal cancer; NR; coloplasty (+LAR); 0	Comparison group 1: 49; 36:2; M=60.2; low rectal cancer; NR; straight anastomosis (+LAR); 0 Comparison group 2: 137; 79:36; M=60.2; low rectal cancer; NR; J-pouch (+LAR); 0	Multicenter RCT at T0: 4m; T1: 12m; T2: 24m	Urinary and bowel function (study-specific)
Hess (2017), Switzerland (31)	51 (40:11); Me=61; locally advanced rectal cancer; 46 T3, 5 T4, 11 N0, 37 N1, 3 N2; preoperative radiochemotherapy and TME with sphincter preservation; NR	NA	Multicenter, prospective, single-arm study at T1: 6m; T2: 12m; T3: 18m; T4: 24m; T5: 30m; T6: 36m	Satisfaction with bowel and urinary function (study-specific)
Ho (2002), Singapore (32)	44 (26:18); M=68.3; mid and low rectal cancer; 6 stage I, 17 stage II, 12 stage III, 9 stage IVT2N0M1, 4 T3N0M1, 2 T3N1M1, 1 T3N2M1, 1 T4N2M1; J-pouch surgery (+ultra LAR); 0	44; 27:17; M=65.4; mid and low rectal cancer; 10 stage I, 14 stage II, 13 stage III , 7 stage IV; coloplasty pouch surgery (+ultra LAR); 0	Single-center RCT at T0: 4m; T1: 12m	Bowel function (study-specific)
King (2008), UK (48)	41 (23:18); M=72.3; 27 colon and 14 rectal cancer; 9 stage I, 19 stage II, 13 stage III; LAP (APR, LAR, hemicolectomy, sigmoid colectomy); 16	19; 8:11; M=70.4; 14 colon and 5 rectal cancer; 1 stage I, 11 stage II, 7 stage III, open (APR, LAR, hemicolectomy, sigmoid colectomy); 5	Single-center RCT at T0: 12 days post-Tx; T1: 6w; T2: 3m; T3: 6m; T4: 12m	Daily activities (study-specific)
Land (2007), USA (52)	206 (129:77); M=58.3; stage II or III colon cancer; fluorouracil and leucovorin (FULV); NR	189; 111:78; M=56.8; stage II or III colon cancer; FULV with oxaliplatin (FLOX); NR	Multicenter RCT at T1: week 4 of treatment; T2: 6m; T3: 12m; T4: 18m	Neurotoxicity (NTX-12)
Law (2021), Australia (54)	117 (80:37); M=61.7; rectal cancer; 9 T1, 38 T2, 70 T3; laparoscopic-assisted resection; NR	111 (74:37); M=61.7; rectal cancer; 3 T1, 40 T2, 69 T3; Open resection; NR	Multicenter RCT at T0: preoperative; T1: 3 m; T2: 6m; T3: 12m	Return to work
Liu (2016), China (33)	58 (38:29); Me=56 (30-70); low and ultra-low rectal cancer; 5 stage I-II, 56 stage III, ; LAP TME+sphincter preserving surgery; 0	39; 19:26; Me=53 (27-75); low and ultra-low rectal cancer; 1 stage I-II, 42 stage III; Open TME+sphincter saving surgery; 0	Multicenter retrospective study at T0: 6m; T1: 12m; T2: 24m; T3: 36 (no prevalence reported at T3)	Bowel function (GQOLI) Urinary function (IPSS) Male sexual function (IIEF) Female sexual function (study-specific)
Machado (2003), Sweden (34)	50 (27:23); Me=67 (38-83); rectal cancer; 10 stage I, 17 stage II, 21 stage III; colonic J-pouch (+LAR); 1	50; 32:18; Me=66.5 (40-87); rectal cancer; 14 stage I, 19 stage II, 17 stage III; side-to-end anastomosis surgery (+LAR); 2	Single-center RCT at T0: pre-Tx; T1: 6m; T2: 12m	Bowel/anal function (modified functional questionnaire)
Marijnen (2005), Netherlands (41)	497 (318:179); Me=64; rectal cancer; 203 stage 0-I, 149 stage II, 145 stage III; PRT+TME (LAR or APR); NR	493; 307:186; Me=64; rectal cancer; 169 stage 0-I, 140 stage II, 157 stage III; TME only (LAR or APR); NR	Multicenter RCT at T0: pre-operative; T1: 3m; T2: 6m; T3: 12m; T4: 18m; T5: 24m	Sexual function (Rotterdam Symptom Check List+additional items)
Matsuda (2015), Japan (35)	51 (33:18); Me=69 (45-85); rectal cancer; 2 T0, 7 T1, 15 T2, 23 T3, 4 T4; high ligation inferior mesenteric artery surgery (+LAP or open LAR); 20	49; 34:15; Me=67 (45-89); rectal cancer; 0 T0, 17 T1, 17 T2, 13 T3, 2 T4; low ligation inferior mesenteric artery surgery (+LAP or Open LAR); 19	Single-center RCT at T0: 3m; T1: 12m	Bowel function (FIQL)

Mols (2018), Netherlands[b] (50)	2625 (1447:1178); M=69.4; 1605 colon and 1020 rectal cancer; 780 stage I, 948 stage II, 722 stage III, 113 stage 4, 62 unknown; any treatment (+chemotherapy in 29.3%, and radiotherapy in 30.6%); NR	315 (age/gender matched normative group); 173:142; M=67.4; NA; NA; NA; NA	Longitudinal, population-based cohort study (Netherlands Cancer Registry) at T0: first year of the study, T1: second year, T2: third year; T3: fourth year	Mental health (HADS)
Paul (2016), Australia (49)	539 (280:259); 75.2% aged 60y+; colorectal cancer; 67% stage I/II, NR	NA	Multicenter prospective, longitudinal study at T0: baseline within 6-12 months post-diagnosis, T1: 12m FU	Mobility, self-care, usual activities, pain/ discomfort, anxiety/ depression (EQ-5D 3L)
Planellas (2020), Spain (36)	35 (23:12); Me=68 (46-94); rectal cancer; 1 stage I, 5 stage IIA, 0 stage IIB, 6 stage IIIA, 14 stage IIIB, 13 stage IIIC, 5 stage IV; end-to-end technique for colorectal anastomosis; 10	30 (17:13); Me=64 (27-81); rectal cancer; 3 stage I, 0 stage IIA, 0 stage IIB, 1 stage IIIA, 5 stage IIIB, 11 stage IIIC, 5 stage IV; side-to-end technique for colorectal anastomosis; 9	Single-center RCT at T0: pre-Tx, T1: 1m, T2: 6m, T3: 12m	Low anterior resection syndrome (LARS), i.e., gas incontinence, incontinence of liquid stool, frequency of bowel movements, clustering of stools, and urgency (LARS questionnaire)
Saito (2015), Japan (42)	209 (209:0); Me=62(56-69); rectal cancer; 3 T2, 169 T3-T4 (only stage II and III included but number of patients NR); N0 94, N1-2 77; LAR or APR; NR	204; 204:0; Me=61 (55-66); rectal cancer; 2 T2, 169 T3-T4; N0 95, N1-2 77; LAR or APR+lateral lymph node dissection; NR	Multicenter RCT at T0: preoperative; T1: 12m	Erectile dysfunction (IIEF-5)
van Duijvendijk (2002), Netherlands (37)	20 (16:4); M=65 (38-83); rectal cancer; 1 stage 0 , 7 stage I, 9 stage II, 3 stage III; TME; NR	14; 9:5; M=69 (38-85); rectal cancer; ; 2 stage I; 5 stage II; 7 stage III; TME+PRT; NR	Single-center prospective, longitudinal study at T0: 1w pre-Tx (surgery or radiotherapy); T1: 4m; T2: 12m	Bowel and urinary function (study-specific)
Van Erning (2016), Netherlands (53)	27 (16:11); 16=70-74y, 9=75-79y, 2=≥80y; colon cancer; stage III; NR	COMPARISON 1 28; 15:13; 6 70-74y, 11 75-79y, 11 ≥80y; colon cancer; stage III; NR COMPARISON 2 58; 26:32; 6 70-74y, 24 75-79y, 28 ≥80y; colon cancer; stage III; NR	Multicenter prospective, longitudinal study at T1: postoperative, T2: 6m postoperative, T3: 12m postoperative	Sensory symptoms, motor symptoms, autonomic symptoms (QLQ-CIPN20)
Vardy (2016), Australia (51)	173 (117:56); Me=57.0 (23-75); 104 colon cancer, 66 rectal cancer; 2 stage I, 46 stage II, 125 stage III, 0 stage IV; surgery and adjuvant/ neoadjuvant chemotherapy (54 5FU, 72 oxaliplatin, 44 chemoradiation, 3 missing); NR	COMPARISON 1 116; 66:50; Me=60.5 (23-75); 89 colon cancer, 27 rectal cancer; 48 stage I, 60 stage II, 3 stage III, 0 stage IV; surgery without chemotherapy; NR COMPARISON 2 73; 40:33; Me=55.5 (28-75); 54 colon cancer, 16 rectal cancer; 0 stage I, 0 stage II, 4 stage III, 69 stage IV; NR; NR	Multicenter prospective, longitudinal study at T0: pre-chemo (if given), T1: 6m, T2: 12m, T3: 24m	Fatigue (FACT-F) Anxiety/depression (FACT-G)
Varpe (2009), Finland (38)	74 (total sample; subgroup sample size NR) (21:26); M=68 (42-86); rectal cancer; 10 stage I, 21 stage II, 16 stage III; LAR; 0	74 (total sample; subgroup sample size NR); 12:10; M=69 (44-84); rectal cancer; 5 stage I, 7 stage II, 10 stage III; APR; 0	Single-center prospective, longitudinal study at T0: pre-Tx; T1: 12m	Anal, urinary and sexual function (study-specific)

Wang (2015), China (43)	71 (71:0); M=60.3 (36-68); rectal cancer; 9 stage 0/I, 22 stage II, 40 stage III; robotic TME LAR; 0	66; 66:0; M=58.7 (36-71); rectal cancer; 8 TME stage 0/I, 24 stage II, 34 stage III; human LAP TME LAR; 0	Single-center prospective, longitudinal study at T0: pre-Tx; T1: 12m	Male sexual function (IIEF)

M=mean; Me=median; w=week; m=month; NR=not reported; NA=not applicable; PRO – patient-reported outcome; PROM – patient-reported outcome measure; RCT – randomized clinical trial; PRT – preoperative radiotherapy; Tx – treatment; LAP – laparoscopic; LAR – low anterior resection; APR – abdominoperineal resection; TME - total mesorectal excision; TAMIS – transanal minimally invasive surgery; AR – anterior resection;

[a]Cancer stage converted to TNM system where possible (or as much of the TNM system as possible) but otherwise IUCC staging.

[b]Only includes PROs and PROMs that reported prevalence rates.

Table 2: Prevalence of patient-reported outcomes (PROs) captured across assessment time-points from baseline (before treatment) up to the five-year follow-up in survivors of rectal cancer, colon cancer, and mixed populations.

PROs (PROMs)	Baseline pre-Tx	<1mo post-Tx	1-2mo post-Tx	>2-4mo post-Tx	>4-8mo post-Tx	>8-12mo post-Tx	>12-18mo post-Tx	>18-24mo post-Tx	>24-36mo post-Tx	>36-60mo post-Tx
Mental health										
Anxiety and depression (EQ-5D, HADS, FACT-G)										
Rectal cancer (EQ-5D) (45)	3-42%	1-47%			0-29%	0-32%	3-42%	1-47%		
Colon cancer (47,49)	24-50%			30-40%	35-56%		25-30%		21-30%	
Mixed (46,50,51)	11-43%			31-35%	8-39%	5-40%		4-29%		
Bowel function										
Problems with overall defecation function										
Rectal cancer (study-specific, GIQLI, LARS) (33, 35, 36, 38)	17-34%		30-64%	38-39%	40-58%	16-53%		5-9%		
>3 bowel movements per day (study-specific, MSKCC)										
Rectal cancer (study-specific) (25,31,32,35)				21-62%	19-54%	25-29%	25%	22%	20-22%	2-20%
Colon cancer (26)	13%				31%	30%				
Inability to differentiate gas and stool										
Rectal cancer (study-specific, modified functional questionnaire) (25, 32, 34, 35)	2-22%			8-84%	16-84%	11-89%			7-12%	
Inability to defer defecation										
Rectal cancer (study-specific, modified-functional questionnaire) (25, 34)	88-90%				43-64%	47-68%			13-17%	
Sensation of incomplete defecation										
Rectal cancer (study-specific, modified functional questionnaire) (25, 32, 34, 35, 37)	0-50%			36-60%	14-60%	34-67%			0-33%	
Tenesmus										

Rectal cancer (study-specific) (32, 37)	28-71%	0-54%		3-50%				
Fecal incontinence								
Rectal cancer (study-specific, FISI, EORTC QLQ-CR29) (25, 27-29, 37)	20-57%	3-85%	0-55%	9-71%	28-40%	30-40%	0-83%	20%
Inability to evacuate bowel in under 15 mins								
Rectal cancer (modified functional questionnaire, study-specific) (25, 34, 35)	96-98%	75-80%	57-81%	68-84%			90-96%	
Loss of large quantities of stools								
Rectal cancer (study-specific) (37)	0%	8-20%		0-14%				
Dissatisfaction with bowel function								
Rectal cancer (study-specific) (25, 31, 35)		15-61%	0-25%	5-20%	18%	14%	0-12%	0-10%
Use of bowel medication								
Rectal cancer (modified functional questionnaire, study-specific) (25, 32, 34, 35)	0-16%	2-30%	2-33%	0-33%			5-37%	
Pad usage								
Rectal cancer (study-specific, modified functional questionnaire) (30, 34, 35, 37)	14-29%	43-100%		20-77%		54-73%		
Adverse impact of bowel function on daily life								
Rectal cancer (modified functional questionnaire) (34)	0-4%							
Food restriction due to bowel function								
Rectal cancer (study-specific) (25)			36-40%				10-11%	
Nocturnal bowel movement								
Rectal cancer (study-specific) (32, 35)		3-41%		9-36%				
Rectal pain								
Rectal cancer (EORTC QLQ-CR29) (29)	30%					20%	15%	5-20%
Blood in stool								
Rectal cancer (EORTC QLQ-CR29) (29)	45%					80%	75%	40-60%
Perineal excoriation								
Rectal cancer (study-specific) (32)		3-14%		9-13%				
Flatulence								
Rectal cancer (EORTC QLQ-CR29) (28)	70-75%	68-78%	60-80%	70-85%	85-86%	70-72%	70-75%	
Urgency of defecation								

Rectal cancer (study-specific) (25, 30, 35, 37)	14-21%			61-82%		17-90%			70-79%			
Sexual function												
Sexual activity												
Rectal cancer (Rotterdam Symptom Checklist supplemented with additional items, FSI) (39, 41)	50-81%			26-72%	24-83%	36-87%	70-89%		67-90%			
Sexual dissatisfaction												
Rectal cancer (study-specific) (38)	43-61%					45%						
Erectile dysfunction (IIEF-5, IIEF, EORTC QLQ-CR29, EORTC QLQ-CIPN20)												
Rectal cancer (28, 39, 40, 42, 43)	24-88%			32-70%	42-83%	27-93%	70-78%		68-78%			
Colon cancer (53)	77%				88%	79%						
Ejaculatory dysfunction												
Rectal cancer (IIEF-5) (39)	22%			78%	70%	67%						
Lubrication problems												
Rectal cancer (FSI) (39)	52%			83%	50%	62%						
Dyspareunia												
Rectal cancer (FSI) (39)	36%			75%	67%	48%						
No sexual interest (males)												
Rectal cancer (EORTC QLQ-CR29) (28)	20-22			43-33%	18-30%	15-19%	19-25%		19-20%			
Sexual arousal (females)												
Rectal cancer (FSI) (39)	39%			67%	67%	57%						
Physical functioning												
Problems with mobility												
Rectal cancer (EQ-5D) (45)	9-12%	1-34%			0-14%	0-13%						
Colon cancer (EQ-5D)(47, 49)	15-74%			60-80%	60-70%		55-70%			55-65%		
Mixed (EQ-5D) (46)	23-33%			25-33%	37-39%	31-34%			33-43%			
Problems with daily activity including self-care												
Rectal cancer (EQ-5D) (45)	0-15%	1-48%			0-24%	0-55%						
Colon cancer (EQ-5D) (47, 49)	3-27%			5-60%	10-74%		5-40%			5-45%		
Mixed (EQ-5D) (46)	9-33%			18-43%	17-41%	11-34%			10-48%			
Return to cooking												
Mixed (study-specific) (48)		0-10%	47-61%	63-76%	79-85%	89-90%						
Return to driving												

Mixed (study-specific) (48)		0-5%	32-60%	79-80%	79-80%	80-84%				
Return to shopping										
Mixed (study-specific) (48)		0%	0-24%	39-53%	39-53%	1-53%				
Return to housework										
Mixed (study-specific) (48)		0%	11-20%	58-61%	1-61%	61-68%				
Urinary function										
Problems with overall urinary function										
Rectal cancer (IPSS, study-specific, unknown) (38, 39)	22-42%			30%	20%	17-51%		50%		
Urinary incontinence										
Rectal cancer (study-specific, EORTC QLQ-CR29) (28, 29, 37)	0-42%			10-50%	18-35%	18-52%	25-30%	15-35%	20%	5-10%
Other symptoms										
Pain/discomfort										
Rectal cancer (EQ-5D, EORTC-QLQ-C30) (28, 45)	2-49%	2-68%		55-58%	1-52%	1-44%	37-38%	33-35%		
Colon cancer (EQ-5D)(47, 49)	26-45%			45%	45-74%		25-45%		40%	
Mixed (EQ-5D) (46)	30-33%			40-45%	39-41%	31-37%		42-48%		
Fatigue										
Rectal cancer (EORTC QLQ-C30) (28)	55-68%			82-85%	62-85%	61%	65-70%	65-70%		
Mixed (FACT-F) (51)	59%				64%	43%		33%		
Insomnia										
Rectal cancer (EORTC QLQ-C30) (28)	45-50%			55-58%	42-58%	35-39%	35-50%	40-42%		
Tingling/numbness in hands or feet										
Colon cancer (EORTC QLQ-CIPN20, FACT&GOG-NTX-12) (52, 53)	7-12%	5-55%			5-49%	10-32%	6-36%			
Numbness in hands or feet										
Colon cancer (EORTC QLQ-CIPN20) (53)	7-12%				17-20%	15-17%				
Aching or burning pain in hands or feet										
Colon cancer (EORTC QLQ-CIPN20) (53)	4%				5-12%	6-9%				
Trouble distinguishing hot and cold water										
Colon cancer (EORTC QLQ-CIPN20) (53)	3%				5%	6%				

Trouble standing/walking					
Colon cancer (EORTC QLQ-CIPN20, FACT&GOG-NTX-12) (52, 53)	7%	3-5%	4-16%	5-11%	5-7%
Feeling weak all over					
Colon cancer (FACT&GOG-NTX-12) (52)		25-27%	10-12%	7-8%	9-10%
Trouble feeling shapes					
Colon cancer (FACT&GOG-NTX-12) (52)		2-3%	4-17%	3-4%	2-8%
Trouble with buttons					
Colon cancer (FACT&GOG-NTX-12) (52)		5%	3-11%	4-6%	2-4%
Trouble standing/walking due to weakness in legs					
Colon cancer (EORTC QLQ-CIPN20) (53)	16%		21%	20%	
Trouble driving					
Colon cancer (EORTC QLQ-CIPN20) (53)	7%		11%	4%	
Hand/food pain in cold water					
Colon cancer (FACT&GOG-NTX-12) (52)		6-65%	8-25%	6-16%	8-22%
Trouble hearing					
Colon cancer (EORTC QLQ-CIPN20, FACT&GOG-NTX-12) (52, 53)	3-16%		9-19%	10-13%	7-21%
Ringing Ears					
Colon cancer (FACT&GOG-NTX-12) (52)		5-12%	7-9%	4-5%	6-11%
Cramps in hands or feet					
Colon cancer (EORTC QLQ-CIPN20) (53)	7-9%		12-17%	14-18%	
Trouble holding a pen/small object					
Colon cancer (EORTC QLQ-CIPN20) (53)	7-15%		12-24%	10-22%	
Trouble opening a jar					
Colon cancer (EORTC QLQ-CIPN20) (53)	19%		24%	20%	
Blurry vision					
Colon cancer (EORTC QLQ-CIPN20) (53)	10%		16%	9%	
Dizziness after standing up					

Colon cancer (EORTC QLQ-CIPN20) (53)	13%		13%	12%		
Joint pain/muscle cramps						
Colon cancer (FACT&GOG-NTX-12) (52)		12-17%	14-20%	16-22%	16-21%	
Foot/hand discomfort						
Colon cancer (FACT&GOG-NTX-12) (52)		8-24%	7-30%	11-18%	5-22%	
Anal itching or burning						
Rectal cancer (Modified Functional Questionnaire) (34)	14-16%		16-20%	5-16%		14-16%
Return to work						
Rectal cancer (study-specific) (54)	Full-time[a] (40%) Part-time[b] (13%)			Full-time[a] (28%) Part-time[b] (6%)		

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core30; EORTC QLQ-CR29, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Colorectal29; EORTC QLQ-CIPN20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy Induced Peripheral Neuropathy; EQ-5D – EuroQol-5Dimensions; FACT&GOG-NTX-12 – Functional Assessment of Cancer Therapy & Gynecologic Oncology Group – Neurotoxicity 12; FISI – Fecal Incontinence Severity Index; FIQL – Fecal Incontinence Quality of Life; FSI – Female Sexual Index; GIQLI – Gastrointestinal Quality of Life Index; HADS – Hospital Anxiety and Depression Scale; IIEF-5 – International Index of Erectile Function; IPSS – International Prostatic Symptom Score; LARS – Low Anterior Resection Syndrome questionnaire; SF-36 – 36-Item Short Form Survey.

[a]Percentage of people returning to full-time work (of those who were working full-time preoperatively).

[b]Percentage of people returning to part-time work (of those who were working part-time preoperatively).

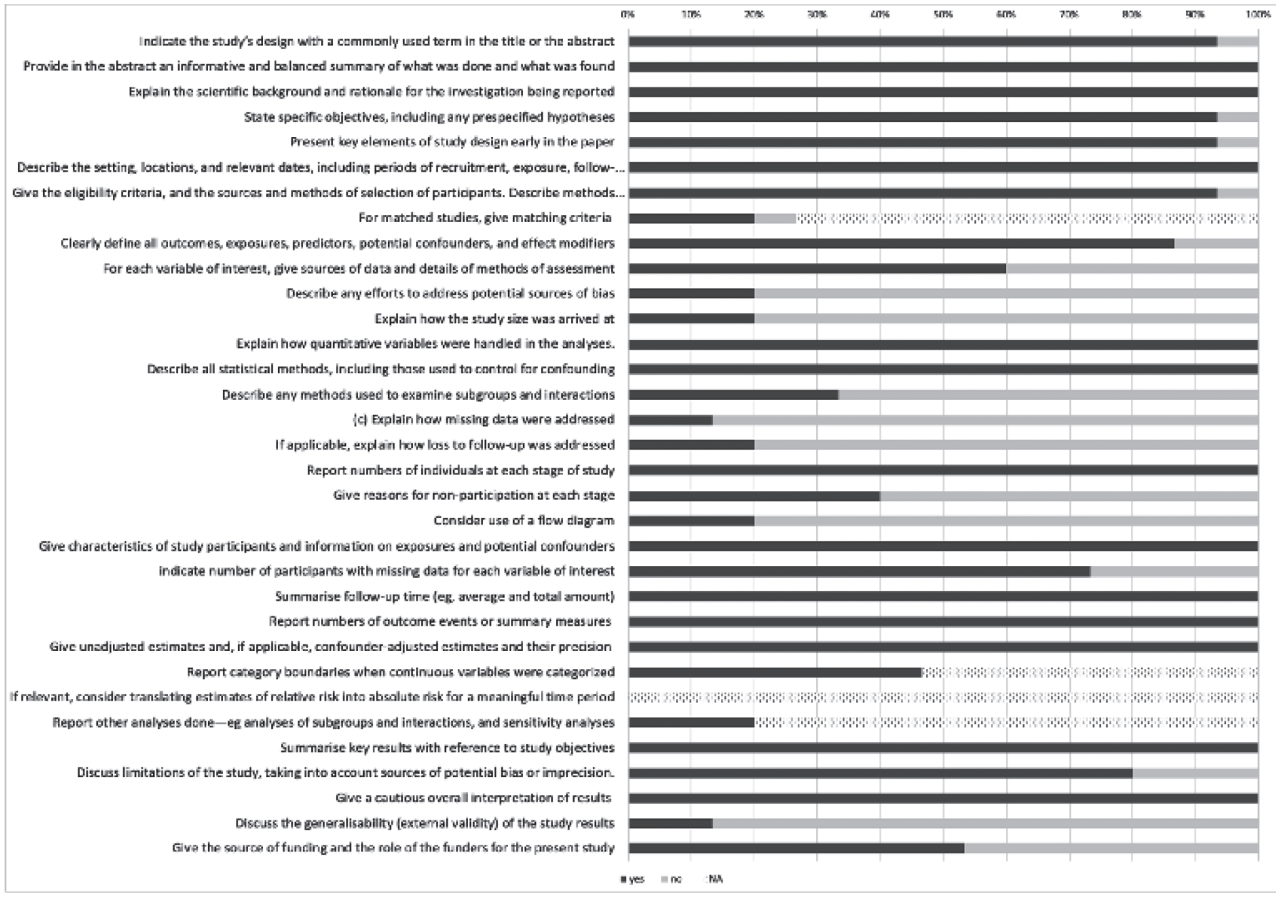

Figure 3: Quality assessment of n=15 longitudinal cohort studies using STROBE checklist.

PROs were assessed with three generic and 14 disease-specific measures. Eight study-specific measures were used. Online supplement 2 provides information about the PRO measures used and the domains assessed across the studies.

Prevalence of Patient-reported Outcomes (PROs)

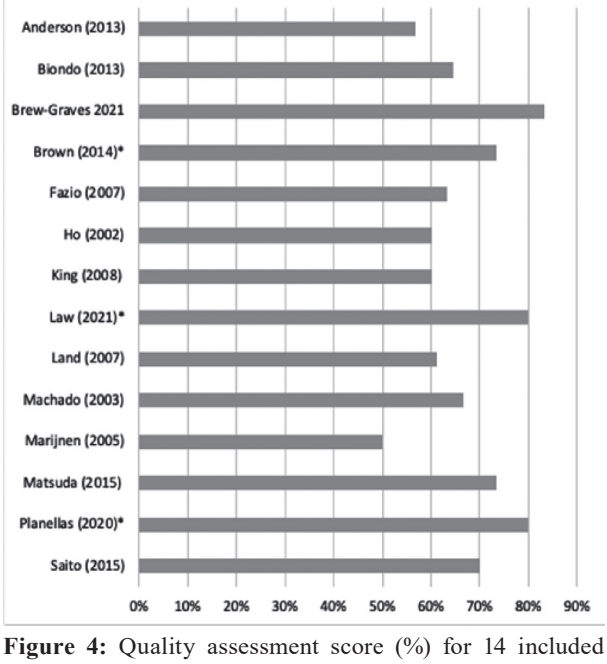

Figure 4: Quality assessment score (%) for 14 included randomized controlled trials, ranked by score (not including N/A). *Substudy of RCT - quality assessment of methods as reported elsewhere (e.g. RCT protocol, original RCT paper)

Table 2 shows the range of prevalence rates for PROs described in the included studies across a range of assessment time points from baseline (pre-treatment) to five years post-treatment for rectal, colon, and mixed colorectal cancer. None of the included studies assessed PROs beyond five years. For many PROs and time-points, a wide prevalence range was reported across studies.

Bowel Function

Across the 15 studies that examined bowel function (25-38), 16 aspects were assessed. Among rectal cancer survivors, 18% were dissatisfied with their bowel function at 12 months (31, 35), and up to 10% were dissatisfied more than three years post-treatment (25, 31, 35). Fecal incontinence was reported by 20% (29) of rectal cancer survivors, and 2-20% reported having greater than three bowel movements a day more than three years following primary treatment (25, 31, 32, 35). One study stated that 5-37% of rectal cancer survivors used medications to manage these bowel problems at two to three years post-treatment (25). Among colon cancer survivors, 30% reported having more than three bowel movements a day 12 months post-treatment (26).

Urinary Function

Urinary function was assessed in six studies (28, 29, 37-40). For survivors of rectal cancer, overall urinary function was problematic for 22-42% at baseline (28, 29, 37-40) and 17-51% at one year

Figure 5: Quality assessment of n=14 randomized controlled trials using CONSORT checklist.

following treatment (28, 37-39). At two years post-treatment, one study reported that 50% of rectal cancer survivors experienced problems with their urinary function, and 20% continued to experience urinary incontinence at three years post-treatment (29). No data on urinary function was available for survivors of colon cancer or mixed populations.

Sexual Function

Seven aspects of sexual function were assessed in eight studies (28, 29, 33, 35, 38-44). In male survivors of rectal cancer, erectile dysfunction was reported in 68-78% at two years post-treatment (28, 40). One study reported dyspareunia and lubrication problems in 48% and 62% of female survivors of rectal cancer, respectively (39). No data on sexual function was available for survivors of colon cancer or mixed populations.

Physical Function

Physical function was assessed in five studies (45-49). At one year post-treatment, 2-55% and 0-13% of rectal cancer survivors reported daily activity and mobility problems, respectively (45). In survivors of colon cancer, 5-45% and 55-65% patients reported problems with daily activities and mobility, respectively, at three years following treatment (46). In studies involving a mixed population of colon and rectal cancer patients, 80-84% survivors reported returning to driving (48), and 31-34% reported problems with mobility (46) at one year post-treatment.

Depression and Anxiety

Depression and anxiety were assessed in six studies (45-47, 49-51). One study reported anxiety and depression in 1-47% of rectal cancer survivors two years post-treatment (45). In survivors of colon cancer, 21-30% reported anxiety and depression (47). In mixed population studies, 5-40% patients reported anxiety and depression at one year following treatment (46, 50, 51).

Pain/Discomfort

Five studies assessed general pain and discomfort (28, 45-47, 49). At baseline, 2-41% of rectal cancer (28, 45), 26-45% of colon cancer (47, 49), and 30-33% of mixed colorectal cancer survivors (46) reported general pain and discomfort. General pain was reported in 33-35% of survivors of rectal cancer (28) and in 42-48% of survivors in mixed populations (46) at two years post-treatment, and 40% of survivors of colon cancer at three years (47).

Fatigue

Two studies assessed fatigue (28, 51). Before surgery, 55-68% of rectal cancer survivors reported fatigue, and 65-70% continued to report fatigue at two years post-treatment (28). One study with a mixed population reported baseline fatigue of 59%, which fell to 33% by two years post-treatment (51).

Neuropathic Symptoms

Tingling and numbness in hands or feet were assessed in two studies (52, 53) involving colon cancer survivors. Two years post-treatment, 6-36% of patients reported tingling and numbness in hands or feet.

Return to Work

In rectal cancer survivors, one study reported that 68% returned to their preoperative work status by 12 months after primary treatment (54).

CRC survivors continue to experience a range of symptoms and functional impairments long after their primary treatment has been completed. At 12 months post-treatment, up to 94% of survivors experienced some form of bowel dysfunction, including an inability to differentiate gas and stool and inability to defer defecation. None of the included studies highlighted whether a continence service was accessed. Problems with sexual function were also highly prevalent. Up to 78% of men experienced erectile dysfunction even at two years, and 48% of women reported dyspareunia at 12 months post-treatment. Physical functioning, including self-care, was impaired in up to 65% of survivors at three years following treatment. At two

years post-treatment, problems with bowel and sexual function remained highly prevalent. Pain and fatigue persisted at two years post-treatment in up to 48% and 70% of survivors, respectively. Of note, the majority of the studies included survivors of rectal cancer, who are more likely than colon cancer patients to receive radiation therapy. This is an important consideration as radiation therapy near the pelvic organs can cause pelvic nerve injury, leading to various bowel, urinary, and sexual problems. Rectal cancer patients are also more likely to have a stoma, which comes with its own challenges.

As evident from the findings of this review, some PROs cause persistent problems despite the common belief that symptoms subside shortly after treatment (55). Such findings complement the existing literature about post-treatment CRC survivorship. Qualitative studies highlight the ongoing burden of symptoms beyond the first year following treatment completion (7). Quantitative findings demonstrate the severity of the impairment in physical and psychological functioning experienced by survivors in their day to day lives, which can persist even up to 14 years following treatment (4, 55-57). Our findings also highlight a gap in the existing literature, where more longitudinal studies with follow-up periods greater than three years are required to examine PROs in CRC survivors by treatment type. In particular, future research should explore social and cognitive function, as long-term prevalence data on these PROs is lacking. Qualitative studies suggest ongoing bowel problems limit one's ability to participate in social activities due to challenges such as need for toilet facilities and fear of bowel-related accidents (7). Despite these social challenges, we did not find any studies reporting longitudinal data on the prevalence of social functioning in CRC survivors.

There is a need for a mechanism to identify the high-need survivors who have ongoing but unmanaged problems such as anxiety, depression, pain, neuropathy, urinary and bowel disorders, and sexual dysfunction and could benefit from supportive care interventions. Investigating the PROs that are highly prevalent and persistent has important implications for clinical practice. Knowledge of these PROs enables clinicians to be mindful of and monitor any problems that may arise. It can also inform the development and referral of appropriate services in the community to improve the lives of CRC survivors. Currently, survivors report using a trial-and-error approach in an attempt to self-manage issues that are not addressed professionally (7). If not managed properly, these can have detrimental effects on patients' mental and physical health. There is also a need for intimacy/sexual supportive care and interventions for managing fatigue.

Using data from moderate to high-quality studies, our review highlights the long-term prevalence of several symptoms and functional impairments long after primary treatment for CRC. This is contrary to common beliefs that most symptoms and functional impairments resolve after 12 months. However, meta-analysis was not feasible given the heterogeneity in treatment types, time intervals between baseline and follow-up assessments, and PRO instruments used across the included studies. Instead, we used narrative synthesis to describe results for the prevalence of various PROs over time. We only included studies published in English. It is possible that relevant non-English studies have not informed our conclusions. We were limited by how results were reported in some papers, specifically when cancer stages, tumor groups and/or treatment types were combined for reporting, as this obscured any differential group and treatment effects. This is unfortunate, as it is known that some treatments are associated with greater functional impairment than others (4). For instance, survivors who received chemoradiation reported lower physical function and greater adverse colorectal concerns than those who had not (58). Also, we could not summarize prevalence rates for specific surgical techniques as too few studies investigated the same technique. Further work is required to explore the differential effects of treatment types and cancer stages on the longitudinal prevalence of adverse treatment effects.

Conclusion

In conclusion, many CRC survivors experience persistent fatigue, pain, bowel changes, and problems with physical and sexual function. In order to improve their quality of life and provide more effective patient-centered care for CRC survivors, these patient-reported outcomes (PROs) need to be identified and monitored so that effective management strategies can be developed and employed. Improved communication about likely long-term effects and management strategies would enable clinicians to better prepare for and support patients in managing treatment sequelae.

What Does This Paper add to the Literature?

CRC survivors and managing clinicians need greater awareness of likely treatment effects to better prepare for sequelae of treatment. Contrary to common beliefs, CRC survivors experience persistent symptoms and functional impairments long after treatment completion. Monitoring these outcomes would allow earlier detection and amelioration of problems, improving quality of life.

Compliance with Ethical Standards

Ethics approval and consent to participate were not required for this systematic review.

Declarations

Ethics approval and consent to participate were not

required for this secondary analysis.

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