Prevalence and determinants of depression up to 5 years after colorectal cancer surgery:

Results from the ColoREctal Wellbeing (CREW) study

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DATA ACCESSIBILITY

The data underlying this article will be shared on reasonable request to the corresponding author. Information regarding data access is available at http://horizons-hub.org.uk/access_data.html

PRIOR PRESENTATION

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ABSTRACT

Aim:

Depression experienced by people with colorectal cancer (CRC) is an important clinical problem affecting quality of life. Recognition at key points in the pathway enables timely referral to support. This study aimed to examine depression pre- and 5 years post-surgery to examine its prevalence and identify determinants.

Methods:

The ColoREctal Wellbeing (CREW) study is a prospective UK cohort involving 872 adults with non-metastatic CRC recruited before curative-intent surgery. Questionnaires completed pre-surgery, and 3, 9, 15, 24, 36, 48 and 60 months post-surgery, captured socio-demographics, assessed depression (Centre for Epidemiologic Studies Depression Scale, CES-D) and other psychosocial factors. Clinical details were also gathered. We present prevalence of clinically significant depression (CES-D≥20) over time and its predictors assessed pre-surgery and 2 years post-surgery.

Results:

Pre-surgery, 21.0% of the cohort reported CES-D≥20 reducing to 14.7% 5 years post-surgery. Pre-surgery risk factors predicting subsequent depression were clinically significant depression and anxiety, previous mental health service use, low self-efficacy, poor health, having neoadjuvant treatment and low social support. Post-surgery risk factors at 2 years predicting subsequent depression were clinically significant depression, negative affect, cognitive dysfunction, accommodation type and poor health.

Conclusions:

Depression is highly pervasive in people with CRC, exceeding general population prevalence across follow-up. Our findings emphasise the need to screen and treat depression across the pathway. Our novel data highlight key risk factors of later depression at important and opportune time points: pre-surgery and the end of routine surveillance. Early recognition and timely referral to appropriate support is vital to improve long-term psychological outcomes.

WHAT DOES THIS PAPER ADD TO THE LITERATURE?

Depression in people living with colorectal cancer is an important clinical problem. Our study shows that the prevalence of depression exceeds general population prevalence over time. It also highlights risk factors of later depression at important time points (before surgery and end of routine follow-up) which informs strategies for recognition and referral to appropriate psychosocial support.

INTRODUCTION

Depressive disorders are one of the highest contributors to global disease burden, affecting 4% of people(1). Its prevalence is greater in people living with cancer (rates range between 8 and 27%(2)) and thus is a clinical and policy priority(3). In people living with colorectal cancer (CRC), the prevalence of depression is also greater when compared to the general population with rates reaching 37%(4-7). Depression in people living with cancer is associated with poor quality of life (QoL)(8), reduced adherence to treatment(9), reduced survival(10) and is associated with an increased risk of suicide(11). More specifically, people with CRC and depression have poorer QoL, health status and wellbeing after diagnosis and surgery(5, 7).

Despite this, depression is often not identified in people with cancer and few are treated(6); possibly due to a range of factors associated with underreporting mental health issues (e.g. stigma)(12). Timely recognition and referral to support and intervention is recommended in clinical guidelines for depression internationally(13) with UK guidelines recommending targeting screening in people at most risk(14). However, determinants of depression in people living with cancer are poorly characterised(15) with calls for more evidence in people with CRC(16). Identification of people most at risk also informs intervention development, reduces disease burden and improves planning of psychosocial care resources(17).

Several determinants of depression in people with CRC have been described including: female gender(4, 18, 19), low socio-economic status(20), higher stage disease(21), receipt of neoadjuvant and adjuvant treatments(22), and low social support(23, 24). Findings related to age are inconsistent(19, 21, 25) but may be owed to sample characteristics (e.g. recruitment of an older sample(25)). Depressive symptoms in people with CRC are also reported to reduce over time(4, 5) but much research is cross-sectional(16). We conducted a scoping review and found that no published longitudinal studies in people with non-metastatic CRC have examined pre-surgery risk factors associated with reporting depression up to 5 years post-treatment (Appendix 1).

UK clinical guidance recommends pre- and post-treatment as key time points to appraise psychological outcomes in people living with cancer(26). Assessment, close to diagnosis, allows for a better understanding of the impact of cancer and its treatment on depression outcomes(15,

26). Early screening is also encouraged due to its benefits: improving treatment adherence, reducing burden on health services and patients, enhancing communication between clinical teams and patients, and more timely referral to support(17, 27). Addressing psychological outcomes post-treatment gives patients the opportunity to reflect on the impact and psychosocial concerns following the intense scheduling of cancer treatment(15, 26). Post-treatment CRC surveillance is valuable to provide reassurance as patients feel greater concern when its frequency decreases(28), possibly due to reduced contact with clinical teams(29), so we highlight this time point as important to consider. In the UK it is recommended that routine surveillance appointments cease after 2 years(30) with some variation in international guidelines(31).

This paper presents analysis from the ColoREctal Wellbeing study (CREW)(32), a UK prospective cohort investigating factors associated with recovery of health and wellbeing following CRC. Data were collected before and at regular intervals up to 5 years post-surgery. Data comprised of socio-demographic, clinical information, and patient-reported outcomes examining a selection of psychosocial variables (including depression) informed by a conceptual framework of recovery following cancer diagnosis and treatment(33). The analysis assesses 'clinically significant levels' of depression via self-reporting and whilst this is not a 'clinical diagnosis' of depression, which requires a comprehensive assessment accounting contextual factors(14), the cut-off used has high concordance with psychiatric interviews(34) suggesting the experience of high levels of depressive symptomology(35). This paper:

(1) describes the prevalence of clinically significant levels of depression from pre-surgery up to 5 years post-surgery; and,

(2) given the levels of depression pre-surgery and at 2 years post-surgery, identifies which characteristics are associated with subsequent clinically significant levels of depression up to 5 years post-surgery.

METHODS

Study sample

CREW is a prospective cohort study of adults (≥18 years) with non-metastatic colorectal cancer (Dukes' stage A-C) treated with curative-intent surgery. Inclusion and exclusion criteria are published elsewhere(32).

Data collection

Details of study procedures are previously reported(32). Eligible participants were recruited from 29 UK National Health Service (NHS) centres between November 2010 and March 2012. Participants consented and completed questionnaires before surgery (baseline). Follow-up questionnaires were mailed at regular intervals: 3, 9, 15, 24 months and annually up to 5 years post-surgery. Clinical and treatment information was gathered from NHS medical databases at participating centres. Ethical approval was granted by the UK NHS NRES Committee South Central - Oxford B (REC ref: 10/H0605/31). Information collected in the study did not inform the care of the participants involved due to the study design and anonymisation of the data.

Measures

Patient-reported depression was captured using the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D)(36). Higher scores indicate greater levels of depression (range 0-60). A recent meta-review demonstrated that CES-D was responsive to change and suitable for screening for depression in people with cancer(37).

A score of ≥20 has previously been used in studies involving people with cancer to define a 'clinically significant level' of depression(38) and has been shown to be highly concordant with psychiatric interviews(34). A recent meta-analysis examining the screening accuracy of CES-D noted the ≥20 cut-off to be more appropriate when compared to the standard ≥16 cut-off(35). Thus the ≥20 cut-off was selected as an indicator of a clinically significant levels of depression for this study but this does not constitute a formal diagnosis of clinical depression.

Determinants/Covariates

Table 1 lists the validated patient reported outcome measures, socio-demographic questions and clinical information captured pre-surgery and 2 years post-surgery which were used as covariates in the analyses. Covariates are presented according to the conceptual framework domains(33) and the rationale for each measure is provided elsewhere(32). Validated measures were repeated at every time point unless otherwise indicated. Selection of covariates, including EORTC subscales, were informed by our scoping review (Appendix 1). Alongside depression, accommodation type, health status (EQ-5D), age and ethnicity was found to be significantly associated with participant attrition in the CREW study(39) and were included in the model to account for this.

Statistical analysis

Total CES-D score was summarised at each time point using its median and interquartile range to examine changes over time. The number and proportion of participants reporting clinically significant levels of depression (CES-D≥20) were also assessed over time.

Two multivariable logistic regression models were fitted to predict clinically significant levels of depression up to 5 years after surgery (Appendix 2): Model 1 included depression together with other covariates collected pre-surgery (baseline); Model 2 included depression together with other covariates collected at 2 years post-surgery. Multicollinearity was assessed in each model using the Variance inflation factor (VIF). The VIF ranged from 1.05 to 2.18 for Model 1 and from 1.08 to 2.51 for Model 2. VIF below 10 indicates that there was no evidence of multicollinearity in our models.

Missing data were imputed according to published guidelines for the measures selected. If unavailable, these were omitted from the final model. Number of comorbidities were first assessed at 3 months but were included in Model 1 due to its stability over time[40].

A population-average approach was applied to account for the time-varying nature of the binary outcome, where each model was adjusted for the clustering of observations within the participants[41]. Regression analyses were based on a backwards elimination of statistically non-significant predictors. Significance level was fixed at 5% and all analyses were completed in Stata 14.

RESULTS

Sample characteristics

One thousand and eighteen participants were recruited into CREW and 872 consented to questionnaire follow-up. Figure 1 presents the participant flow over follow-up; full details of study recruitment and descriptive statistics are published elsewhere(39, 42). The sample was representative of the eligible patients treated during the recruitment period(39, 42). Table 2 shows demographic and clinical characteristics of the 741 participants who returned a baseline questionnaire and had completed the CES-D with a mean age of 67.54 (SD=10.26). Over 54% of the sample underwent laparoscopic surgery and 40% underwent open surgery for CRC.

Depression over time

At baseline (pre-surgery), people who were women, single, living in rented accommodation and had previously used mental health services, were more likely to report clinically significant CES-D scores (Table 2).

Median scores peaked before surgery at 12.0 (IQR=11.7) and decreased to 9.5 (IQR=12.0) at 5 years (Table 3). Similarly, the proportion of participants reporting clinically significant levels of depression also peaked pre-surgery at 21.0% and reduced to 14.7% at 5 years (Table 3). Overall, 303 participants (34.8%) reported clinically significant depression at least once during their 5 years of follow-up.

Pre-surgery determinants of clinically significant levels of depression

Table 4 presents only the significant pre-surgery factors associated with the likelihood of reporting a clinically significant level of depression.

Participants who reported clinically significant levels of depression pre-surgery had a higher risk of being depressed over follow-up (OR=3.44, 95% CI=2.18–5.45); this was similar for highly anxious people (OR=1.82, 95% CI=1.15–2.87). People with a low level of self-efficacy (confidence) to manage the consequences of a chronic condition were also at a greater risk of reporting clinically significant levels of depression. Conversely, people who reported 'full' social support (OR=0.41, 95% CI=0.23–0.74) had lower odds of reporting clinically significant depression and this was also the case for 'perfect' health status (OR=0.42, 95% CI=0.24–0.75).

Greater risk of reporting clinically significant levels of depression up to 5 years post-surgery were found in people who underwent neoadjuvant treatment (OR=2.99, 95% CI=1.75–5.09) and in those who reported previous use of mental health services (OR=3.33, 95% CI=1.48–5.24) compared to those who did not. People with rectal cancer also had lower odds of having clinically significant depression compared to those with colon cancer (OR=0.55, 95% CI=0.35–0.87).

Both age and domestic status were found to be statistically significant predictors of subsequent clinically significant depression. Younger participants (<51 years old) were at greater

risk of experiencing clinically significant levels of depression when compared to people aged 61-70 (OR=0.50, 95% CI=0.26–0.97), although this was not evident when compared to other age groups (Table 4). The odds of reporting clinically significant levels of depression were two times higher for people who did not have a partner (OR=2.02, 95% CI=1.32–3.09) compared to those who did.

Determinants 2-years post-surgery

Table 5 presents only the significant predictors, captured at 2 years post-surgery, of clinically significant levels of depression reported at 2 years. Similar to pre-surgery, participants reporting clinically significant levels of depression at 2 years were at greater risk of subsequent depression up to 5 years (OR=3.14, 95% CI=1.41–7.04). Those who had higher scores for negative affect were also at greater risk (OR=1.21, 95% CI=1.08–1.36).

People reporting problems with cognitive function (OR=2.21, 95% CI=1.03–4.77) and poorer wellbeing (OR=2.40, 95% CI=1.25–4.61) at 2 years also had higher odds of experiencing clinically significant depression later. Participants who did not own their accommodation were also at greater risk of reporting clinically significant depression (OR=2.38, 95% CI=1.23–4.62).

In contrast, the risk of reporting clinically significant levels of depression was lower amongst those who had 'perfect' health status at 2 years (OR=0.28, 95% CI=0.12–0.68).

DISCUSSION

This is the first prospective cohort to examine the prevalence and risk factors associated with clinically significant levels of depression in people with non-metastatic CRC assessed pre- and up to 5 years post-surgery. Our results reveal that clinically significant levels of depression remain a long-term problem for a considerable proportion of people, despite median CES-D scores reducing over time from initial diagnosis. These results are consistent with previous findings(4, 5). For example, our prevalence rates across each time point occur within the range observed by cross-sectional studies of people living with CRC (7−37%(4-7)) and are considerably higher compared to the median prevalence found in the general population (CES-D≥20; 11.8%)(35).

The novelty of this study is the investigation of risk factors of clinically significant levels of depression at two key time points in the cancer care pathway as recommended by UK clinical guidance(26): close to diagnosis (pre-surgery) and when post-treatment routine surveillance ends (2 years post-surgery). Identifying risk factors improves planning of psychosocial care and informs intervention development(17). We identified several pre- and post-surgery risk factors of depression consistent with previous work(4, 5, 7, 19, 20, 22-25).

Importantly, our findings underscore the need for depression screening close to diagnosis with clinically significant levels pre-surgery identified as a risk for later depression. Early screening has been shown to positively impact care by improving more timely referrals for psychological intervention(17, 27). Our analysis at 2 years post-surgery also suggests the need for assessment of depression and depressive symptomology (negative affect) when post-treatment surveillance ends. Regular appraisal of psychological needs throughout the pathway aligns with recent emphasis of risk stratification in the UK NHS Long Term Plan to inform personalised care for people with cancer and facilitate referral to appropriate levels of care(43). Psychosocial interventions for people with colorectal cancer have been reported to be beneficial in improving depression and anxiety symptomology, as well as QoL (44, 45). Novel strategies for follow-up have been tested in Australia(46) , Canada(47) and are being considered in the USA(48). Such strategies can help target specialist resources as these become increasingly scarce(48). Innovative models of psychological screening and care (e.g. stepped-care and nurse-led collaborative interventions) for people with cancer are effective in reducing psychological

symptoms, improve QoL for people with a depressive or anxiety disorders and are cost-effective(49, 50). Internationally, variability in models and approaches to survivorship care and complexity in reimbursement for psychosocial and integrated care make implementation a challenge(51).

Our pre-surgery analysis also highlights at-risk groups to whom we should direct depression screening. People undergoing neoadjuvant treatment commonly face more complex surgery, stoma formation, additional side effects, and increased treatment time length(22) which can explain our findings and so attention should focus on this group. People with rectal cancer had a lower risk of clinically significant depression over time but no previous CRC studies have reported tumour site as a significant predictor of depression(16). This relationship was also unexpected as people with rectal cancer often have complex treatment regimens (including neoadjuvant treatment)(52) which may impact psychological outcomes, particularly those who later have a permanent stoma(53). One possible explanation could be that a more complex treatment pathway may result in greater contact with clinical teams and this may improve perceptions of support(29, 54) that could help to reduce depression symptomology. Nevertheless, this finding requires further investigation.

Our analysis further recommends that depression screening should target people with a history of mental health problems or with psychological comorbidities (e.g. anxiety). This is unsurprising as levels of anxiety tend to peak close to diagnosis(55) and commonly co-occurs with depression(8).

The value of assessing self-efficacy and social support early in the pathway was highlighted by our pre-surgery analysis. This is important given the increasing role of self-management for people with cancer(56); thus confidence to manage consequences of cancer and its treatment need to be assessed early on. Assessing the level of social support at the point of diagnosis is imperative given its importance for depression outcomes and later QoL(23).

Our analysis at 2 years post-surgery highlighted other at-risk groups in whom assessment and support for depression may be helpful. People with cognitive difficulties post-surgery were at greater risk of later depression which is important as cognitive dysfunction is a commonly reported consequence of CRC treatment(57). However, caution should be applied as it can be

difficult to delineate cognitive dysfunction as a result of cancer treatment or as a symptom of depression and/or anxiety(58). Type of accommodation (rented or other) was also highlighted as a risk factor but this specifically has not been reported previously. It could be used as a descriptor of socio-economic status (SES) which has been noted to be a risk factor for anxiety, depression and distress in people with cancer(20, 59). This highlights the need for additional support for this group as low SES may indicate a low availability of resources important for coping which may result in poorer psychological outcomes(59).

Study strengths include the scale and representative nature of the CREW sample with over 91% of all eligible patients approached to participate(39, 42). Loss to follow-up is expected in cohort studies but our response rates remained high up to 5 years (Figure 1; 71%). Participants who withdrew by 5 years were more likely to report clinically significant depression, were ≥80 years of age, did not own accommodation (renting or other) and were of non-white ethnicity at baseline(39). Therefore, our findings may underestimate the true prevalence of depression among the CRC cancer survivors in the UK. Additionally, our sample represents patients from one type of healthcare system (the UK NHS) whereby access and provision of specialist services are universal and free at the point of delivery.

Patient-reported depression may not account for contextual factors considered in diagnostic interviews(14). Nevertheless, the cut-off used suggested clinically significant levels of depressive symptomology(35) and is highly concordant with psychiatric interviews(34). High prevalence of depression over time may be attributed to its undertreatment(6). However, due to a high level of missing data, as a result of poor self-report of health service use in CREW, we were unable to examine use of psychological treatment which may explain our findings. We examined our mental health service use data in a bivariate analysis with CES-D scores for interest (Appendix 3).

Scoping of the literature (Appendix 2) identifies this is as one of the first studies to include a pre-surgery assessment on a range of socio-demographic, psychosocial and clinical factors and the only one to collect data up to 5 years later to examine risk factors of clinically significant levels of depression. The importance of this work is highlighted by the dearth of evidence examining the long-term psychological impacts in people living with and beyond cancer(3), including people with CRC(16). The need for research into the short- and long-term psychological

impacts of cancer and its treatment has been identified as a Top 10 research priority in the UK(60) and our analysis contributes knowledge to this for two crucial time points in the CRC care pathway.

In summary, our results indicate that depression is an enduring problem in people with non-metastatic CRC even at 5 years after surgery. Before surgery it affects 1 in 5 people and 1 in 7 people at five years after surgery, both of which are higher than reported in the general population. Our findings clearly highlight the need for screening for depression across the pathway to improve depression outcomes in the long-term. Early screening should be focussed on those with mental health histories, high levels of anxiety, low self-efficacy, poor health status, and low levels of support, whilst clinicians should also monitor people who undergo neoadjuvant treatment. The end of routine oncology surveillance is also an opportune time to assess depression symptoms, especially as frequency of contact with clinical teams decreases. At this time point, assessment should focus on people with poor health, a lower SES and problems from treatment (e.g. cognitive dysfunction). Depression in people living with cancer is associated with poor health and wellbeing and has an impact on survival and adherence to treatment, early recognition and treatment may lead to overall improved outcomes for patients.

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Figure 1: CREW study participant flowchart

NOTE

Participants who were not sent a questionnaire because of mental capacity issues or through administrative error remained eligible for the questionnaire at the next time point.

Definitions: *Full consent*: participants consented to questionnaire follow-up and the collection of medical details; *Reduced consent*: participants consented to the collection medical details only.

Abbreviations: F/U: Follow-up; MC: Mental capacity; Q: Questionnaire.

Table 1: CREW study measures presented by conceptual framework domains(33) for regression analysis

Domain	Characteristic of interest	Measure
Pre-existing factors (Socio-demographics)	Age	
	Gender	
	Ethnicity	
	Employment Status†	
	Accommodation type†	
	Deprivation Index	Index of Multiple Deprivation (IMD)(61)
Clinical factors	Tumour site	
	Dukes' stage†	
	Neoadjuvant treatment†	
	Surgery type	
	Adjuvant treatment†	
	Stoma status	
	Number of comorbidities‡	Self-reported measure(40)
	Previous use of mental health services§	
Environmental factors	Domestic status	
	Life Events	List of Threatening Experience Questionnaire (LTE-Q)(62)
	Social support	Medical Outcomes Study - Social Support Survey (MOS-SSS)(63)
Personal factors	Self-efficacy	Self-efficacy for Managing Chronic Disease (SEMCD) scale(64)
		Cancer Survivors' Self-Efficacy Scale (CS-SES)(65)
	Affect	Positive and Negative Affect Schedule Short Form (PANAS-SF)(66)
Psychosocial outcomes	State anxiety¶	State-Trait Anxiety Inventory, State scale (STAI-S)(67)
	Wellbeing	Personal Wellbeing Index–Adult (PWI-A)(68)
	Health Status	EuroQoL 5 Dimensions 3 Levels (EQ-5D-3L)(69)

Domain	Characteristic of interest	Measure
	Quality of Life (QoL)‡	Quality of Life in Adult Cancer Survivors (QLACS) scale(70): *Cancer-Specific Summary Score (QLACS-CSS), Benefit of Cancer (QLACS-BC)*
	Symptoms & Functioning‡	European Organization for Research and Treatment of Cancer quality of life measure (EORTC QLQ-C30)(71): *Function scales: Physical, Emotional, Cognitive, Social Symptom scales: Fatigue, Pain, Insomnia, Financial Worry*

NOTE

† To avoid imprecise estimates from the low counts in the regression analyses two or more groups were merged together: Unemployed and retired (Employment status); renting and other (Accommodation type); Stages C1 and C2 (Dukes' stage); radiotherapy, chemotherapy and both (Neoadjuvant treatment; Adjuvant treatment)

‡ Collected from 3 months onwards. Selection of EORTC subscales was informed by previous work involving people with CRC(7, 22, 24, 25).

§ Self-reported at baseline only.

¶ We used a cut-off of ≥40 to indicate a clinically significant level of anxiety(72).

Items comprising the QLACS-CSS and QLACS-BC were collected from 9 months onwards.

Table 2: Sociodemographic and clinical information comparisons of CES-D<20 and ≥20 reported at baseline (N=741)

Covariates reported at Baseline	n (%)	CES-D<20 n (%)	CES-D≥20 n (%)	*P* value*
Age groups, years				
50 or younger	47 (6.4%)	32 (68.1%)	15 (31.9%)	.073
51-60	113 (15.3%)	83 (73.5%)	30 (26.5%)	
61-70	285 (38.6%)	236 (82.8%)	49 (17.2%)	
71-80	217 (29.4%)	173 (79.7%)	44 (20.3%)	
81 or older	77 (10.4%)	58 (75.3%)	19 (24.7%)	
Gender				
Male	440 (59.4%)	373 (84.8%)	67 (15.2%)	**<.001**
Female	301 (40.6%)	210 (69.8%)	91 (30.2%)	
Ethnicity				
White British	623 (92.7%)	491 (78.8%)	132 (21.2%)	.898
Other ethnic group	49 (7.3%)	39 (79.6%)	10 (20.4%)	
Deprivation (IMD) quintile				
1st quintile (least deprived)	146 (20.1%)	123 (84.2%)	23 (15.8%)	.086
2nd quintile	150 (20.6%)	123 (82%)	27 (18%)	
3rd quintile	142 (19.5%)	113 (79.6%)	29 (20.4%)	
4th quintile	136 (18.7%)	99 (72.8%)	37 (27.2%)	
5th quintile (most deprived)	153 (21%)	114 (74.5%)	39 (25.5%)	
Domestic status				
Married / Living with partner	524 (71.1%)	430 (82.1%)	94 (17.9%)	**<.001**
Single / Widowed / Divorced / Separated	213 (28.9%)	150 (70.4%)	63 (29.6%)	
Employment status				
Employed	201 (27.3%)	158 (78.6%)	43 (21.4%)	.980
Unemployed / Retired	535 (72.7%)	421 (78.7%)	114 (21.3%)	
Accommodation type				
Owner occupied	589 (79.9%)	473 (80.3%)	116 (19.7%)	**.021**
Renting / other†	148 (20.1%)	106 (71.6%)	42 (28.4%)	

Covariates reported at Baseline	n (%)	CES-D<20 n (%)	CES-D≥20 n (%)	*P* value*
Previous use of mental health services				
No	670 (94.5%)	536 (80%)	134 (20%)	**<.001**
Yes	39 (5.5%)	22 (56.4%)	17 (43.6%)	
Tumour site				
Colon	475 (64.4%)	374 (78.7%)	101 (21.3%)	.911
Rectal	263 (35.6%)	208 (79.1%)	55 (20.9%)	
Dukes' stage				
A	109 (14.7%)	93 (85.3%)	16 (14.7%)	.335
B	391 (52.8%)	303 (77.5%)	88 (22.5%)	
C (C1 & C2)	229 (30.9%)	178 (77.7%)	51 (22.3%)	
Could not be determined‡	11 (1.5%)	9 (81.8%)	2 (18.2%)	
Neo-adjuvant treatment (any type)				
No	592 (80.7%)	465 (78.5%)	127 (21.5%)	.649
Yes	142 (19.3%)	114 (80.3%)	28 (19.7%)	
Surgery type§				
Laparoscopic	401 (54.3%)	-	-	-
Open	299 (40.5%)	-	-	
Not available	38 (5.2%)	-	-	
Adjuvant treatment (any type)§				
No	477 (64.6%)	-	-	-
Yes	261 (35.4%)	-	-	
Stoma§				
No	262 (35.9%)	-	-	-
Yes	468 (64.1%)	-	-	
Number of comorbidities¶				
0	168 (27.6%)	143 (85.1%)	25 (14.9%)	.055
1	194 (31.9%)	160 (82.5%)	34 (17.5%)	
2	144 (23.6%)	107 (74.3%)	37 (25.7%)	
3+	103 (16.9%)	78 (75.7%)	25 (24.3%)	

P-values in bold indicate a statistically significant difference at the 5% level.

* Chi-square, χ2

† Other accommodation includes: Temporary accommodation, living in residential or nursing home, living with others (e.g. friends or family)

‡ Dukes' stage could not be determined for 11 Full Consent patients with small tumours following neo-adjuvant therapy

§ Captured from the medical records after Baseline

¶ Self-reported at 3-month

Abbreviations: IMD: Index of Multiple Deprivation

Table 3: Descriptive statistics for the CES-D score and clinically significant level of depression (CES-D≥20) at each time point from pre-surgery to 5 years post-surgery

Time point	*Pre-surgery*	*Post-surgery*						
	Baseline	**3mo**	**9mo**	**15mo**	**24mo**	**36mo**	**48mo**	**60mo**
N	*741*	*642*	*605*	*534*	*483*	*382*	*369*	*319*
CES-D total, Median (IQR)	12.0 (11.7)	11.1 (12.0)	10.0 (13.0)	9.0 (12.0)	9.0 (10.9)	8.0 (11.7)	9.0 (11.0)	9.5 (12.0)
CES-D≥20, n (%)	158 (21.3)	124 (19.3)	106 (17.5)	70 (13.1)	73 (15.1)	49 (12.8)	48 (13.0)	47 (14.7)

NOTE

Abbreviations: CES-D: Centre for Epidemiologic Studies Depression Scale; IQR: Interquartile Range

Table 4: Multivariable logistic regression model of clinically significant depression (CES-D≥20) up to 5 years post-surgery, significant covariates collected pre-surgery (baseline)

Theme Block	Covariates	Odds ratio	95% Confidence Interval	*P value*
Socio-demographic factors	**Age groups, years**			
	50 or younger	REF	-	-
	51-60	0.50	0.22 – 1.10	.086
	61-70	0.50	0.26 – 0.97	**.040**
	71-80	0.55	0.27 – 1.13	.103
	81 or older	0.77	0.33 – 1.80	.550
Clinical and treatment factors	**Tumour site**			
	Colon	REF	-	-
	Rectum	0.55	0.35 – 0.87	**.011**
	Neoadjuvant treatment			
	None	REF	-	-
	Yes, any therapy	2.99	1.75 – 5.09	**< .001**
	Previous use of mental health services			
	No	REF	-	-
	Yes	3.33	1.81 – 6.12	**< .001**
	Unknown	0.65	0.23 – 1.81	.411
Environmental factors	**Domestic status**			
	Married / living with a partner	REF	-	-
	Single / widowed / divorced / separated	2.02	1.32 – 3.09	**.001**
Personal factors	**Self-Efficacy (SEMCD)**			
	Low confidence	REF	-	-
	Moderate confidence	0.42	0.24 – 0.73	**.002**
	Confident	0.35	0.20 – 0.61	**< .001**
	Very confident	0.18	0.08 – 0.37	**< .001**
Psychosocial factors	**Depression (CES-D)**			

<20	REF	-	-
≥20 (Clinical Level)	3.44	2.18 – 5.45	**< .000**
Anxiety (STAI-S)			
<40	REF	-	-
≥40 (High Level)	1.82	1.15 – 2.87	**.010**
Social Support (MOS-SSS)			
<100 (Not full)	REF	-	-
=100 (Full)	0.41	0.23 – 0.74	**.003**
Health Status (EQ-5D-3L)			
Not perfect health	REF	-	-
Perfect health	0.42	0.24 – 0.75	**.003**

NOTE

***P*-values in bold indicate a statistically significant difference at the 5% level. The model controls for the time point of the outcome report (post-surgery 3m to 60m), which was statistically significant.**

Abbreviations: CES-D: Centre for Epidemiologic Studies Depression Scale; EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels; MOS-SSS: Medical Outcome Study Social Support Scale; SEMCD: Self-Efficacy for Managing Chronic Disorders Scale; STAI-S: State-Trait Anxiety Inventory - State Scale

Table 5: Multivariable logistic regression model of clinically significant depression (CES-D≥20) up to 5 years post-surgery, significant covariates collected at 2 years

Theme Block	Covariates	Odds Ratio	95% CI	*P*
Socio-demographic factors	**Accommodation type**			
	Owner occupied	REF	-	-
	Rented / Other	2.38	1.23 – 4.62	**.010**
Personal factors	**Affect (PANAS-SF)**			
	Negative Affect	1.21	1.08 – 1.36	**.001**
Psychosocial factors	**Depression (CES-D)**			
	<20	REF	-	-
	≥20 (Clinical Level)	3.14	1.41 – 7.04	**.005**
	Health status (EQ-5D-3L)			
	Not perfect health	REF	-	-
	Perfect health	0.28	0.12 – 0.68	**.005**
	Wellbeing (PWI-A)			
	≥70 (Good)	REF	-	-
	<70 (Poorer)	2.40	1.25 – 4.61	**.008**
	Cognitive functioning (EORTC QLQ-C30)			
	No problem	REF	-	-
	Some problem	2.21	1.03 – 4.77	**.043**

NOTE

***P*-values in bold indicate a statistically significant difference at the 5% level.**

Abbreviations: CES-D: Centre for Epidemiologic Studies Depression Scale; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core-30 Questionnaire; EQ-5D-3L: EuroQoL 5 Dimensions 3 Levels; PANAS-SF: Positive and Negative Affect Schedule Short Form; PWI-A: Personal Wellbeing Index – Adult

Appendix 1: Scoping review search strategy & key studies identified which involve people with CRC including at least one follow-up time point

Dates literature searches conducted:

- October 2016
- August 2017
- September 2018
- May 2019
- July 2019
- October 2020
- March 2021

Databases searched:

- CINHAL
- APA PsycINFO
- APA PsycARTICLES
- MEDLINE (EBSCO)
- ISI Web of Science

Limiters:

- Date published: 01/01/2010 to 01/10/2020
- English language
- Human studies
- Peer-reviewed

Search terms:

Subject/MeSH Headings used where appropriate

Colorectal neoplasms OR Colorectal cancer

(Colon OR Rectum) AND (neoplasms OR cancer)

Depression OR MM Depression
Anxiety OR MH Anxiety Disorder
"Mental Health"
"Psychological disorder"
"Psychological distress"
"Worry"
MH Stress, Psychological
MH Mental Disorders
MH Fear

Lead author, Year	Country of study	Sample	Assessment time points	Depression measure	Key findings	Comparison to the ColoREctal Wellbeing (CREW) study
Dunn et al., 2013 (1)	Australia	1,884 CRC survivors; stages I-IV	T1: 5 months after diagnosis Follow-up: 12 (T2), 24 (T3), 36 (T4), 48 (T5) and 60 (T6) months post-diagnosis	Brief Symptom Inventory-18 (BSI-18)	• Four trajectories of depressive symptoms: constant low levels, constant high levels, and people who increase from low and those who reduce from high levels. • Males, younger participants, later stage, poor social support and lower education were more likely to experience high levels of depression. • 16.1% of participants were in the 'constant high' level trajectory for depressive symptoms (BSI-18 Depression subscale).	• No pre-surgery assessment of psychological distress. • Recruitment of patients with metastatic CRC.
Hart & Charles, 2013 (2)	USA	139 CRC patients (stages I-IV)	T1: Pre-surgery Follow-up: T2: 6 months, T3: 12 months; T4: 18 months post-	Centre for Epidemiologic Studies Depression Scale (CES-D)	• Mean (SD): T1: 10.45 (8.11), T2: 9.33 (7.80), T3: 9.41 (8.74), T4: 9.49 (9.28) • Older adults reported lower levels of depressive symptoms. Men had fewer depressive symptoms than women.	• The prevalence of clinical levels of depression was not assessed. • No follow-up assessment beyond 18 months post-

Lead author, Year	Country of study	Sample	Assessment time points	Depression measure	Key findings	Comparison to the ColoREctal Wellbeing (CREW) study
			surgery			surgery. • Recruitment of patients with metastatic CRC.
Gonzalez-Saenz de Tejada et al., 2017 (3); Quintana et al., 2018 (4)	Spain	972 CRC patients (including patients in relapse)	T1: Pre-surgery Follow-up: T2: 12 months; T3: 24 months post-surgery;	Hospital Anxiety and Depression Scale (HADS)	• 19.6% of participants reported depression at T1 • Patients with depression improved less than participants not reporting depression or anxiety in all health-related quality of life (QOL) domains (EORTC QLQ-C30) domains. • Overall, few differences in depression symptoms in people undergoing either open or laparoscopic surgery. • Mean (SD) [Laparoscopy vs Open]: T1: 4.28 (4.12) vs 5.33 (4.84); T2: 3.52 (3.85) vs 4.08 (4.31); T3: 3.50 (3.97) vs 4.28 (4.38)	• Recruitment of patients with metastatic CRC. • Recruitment of patients in relapse (CREW excluded patients with previous cancer diagnosis). • No follow-up assessment beyond 24 months post-surgery.
Mols et al., 2018	Netherlands	315 CRC	Annual follow-up (1	Hospital	• Significantly higher prevalence of	• Participants recruited 1 to

Lead author, Year	Country of study	Sample	Assessment time points	Depression measure	Key findings	Comparison to the ColoREctal Wellbeing (CREW) study
(5)		survivors (stages I-IV)	to 4 years): T1: 2010, T2: 2011, T3: 2012, T4: 2013	Anxiety and Depression Scale (HADS)	depression (19.0%, N=2,625) compared to a matched population (12.8%, N=315) during their first assessment. • Reduction in depression symptoms over time with the largest difference identified when examining the first and fourth assessments (mean change -0.89). • Fewer depressive symptoms were reported in people who were older, low QOL and lower physical, role, cognitive, emotional and social functioning.	4 years post-diagnosis. • Recruitment of participants with metastatic CRC.

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Appendix 2: Availability of the covariates in two time points of the regression analyses

Thematic Block	Topic / Measure	Taken time points in separate regression models	
		Baseline (pre-surgery)	2 years post-surgery
Pre-existing factors (Socio-demographics)	Age	+	+
	Gender	+[1]	+[1]
	Ethnicity	+[1]	+[1]
	Employment Status	+	+
	Accommodation type	+	+
	Index of Multiple Deprivation (IMD)	+[1]	+[1]
Clinical factors	Tumour site	+	+
	Duke's stage	+	+
	Neoadjuvant treatment	+	+
	Adjuvant treatment	-	+
	Surgery type	-	+
	Stoma status	-	+
	Number of Comorbidities	+[2]	+
	Previous use of mental health services	+	-
Environmental factors	Domestic status	+	+
	Life Events	-	+
	Medical Outcome Study Social Support Scale (MOS-SSS)	+	+
Personal factors	Self-Efficacy for Managing Chronic Disease 6-Item Scale (SEMCD)	+	-
	Cancer Survivor Self-Efficacy Scale (CS-SES)	-	+
	Positive and Negative Affect Schedule Short Form (PANAS-SF)	+	+
Psychosocial outcomes	Centre for Epidemiologic Studies Depression Scale (CES-D)	+	+
	Quality of Life in Adult Cancer Survivors (QLACS) scale: *QLACS Cancer-Specific Summary Score (QLACS-CSS)*	-	+
	QLACS Benefit of Cancer subscale (QLACS-BC)	-	+
	State-Trait Anxiety Inventory - State scale (STAI-S)	+	+
	Personal Wellbeing Index - Adult (PWI-A)	+	+
	EQ-5D-3L	+	+

Thematic Block	Topic / Measure	Taken time points in separate regression models	
		Baseline (pre-surgery)	2 years post-surgery
	EORTC-QLQ-C30: *Physical functioning*	-	+
	EORTC-QLQ-C30: *Emotional functioning*	-	+
	EORTC-QLQ-C30: *Cognitive functioning*	-	+
	EORTC-QLQ-C30: *Social functioning*	-	+
	EORTC-QLQ-C30: *Fatigue*	-	+
	EORTC-QLQ-C30: *Pain*	-	+
	EORTC-QLQ-C30: *Insomnia*	-	+
	EORTC-QLQ-C30: *Financial Worry*	-	+

KEY

'+' included in regression analysis for time point

'-' indicates excluded from regression analysis for time point due to measure not assessed at time point

NOTE

Data are taken from same time point unless otherwise annotated: [1] data taken from baseline time point, [2] data taken from 3-month follow-up time point

Appendix 3: Self-Reported Health Service Use (*Have you used any of the following health and social services in the last 12 months?*)

Time point (post-surgery)	24 months		36 months		48 months		60 months	
CES-D score	≥20 n (%)	<20 n (%)	≥20 n (%)	<20 n (%)	≥20 n (%)	<20 n (%)	≥20 n (%)	<20 n (%)
n	73	410	49	333	48	321	47	272
Mental Health Services	2 (2.7)	0 (0)	2 (4.1)	1 (0.3)	3 (6.3)	1 (0.3)	1 (2.1)	1 (0.4)
Counselling services	4 (5.5)	2 (0.5)	6 (12.2)	2 (0.6)	2 (4.2)	5 (1.6)	1 (2.1)	2 (0.7)
Psychiatrist	4 (5.5)	2 (0.5)	4 (8.2)	1 (0.3)	3 (6.3)	0 (0)	2 (4.3)	1 (0.4)
Self-help group	5 (6.8)	4 (1.0)	2 (4.1)	5 (1.5)	3 (6.3)	6 (1.9)	3 (6.4)	4 (1.5)

NOTE

Abbreviations: CES-D – Centre for Epidemiologic Studies Depression Scale

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                          ┌─────────────────────────┐
                          │ Approached to participate│
                          │ n=1234                   │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Declined      n=179  │◄─────┼─────►│ Reduced consent      │
└──────────────────────┘      │      │ participation        │
                              │      │ n=146                │
                              │      └──────────────────────┘
                          ┌─────────────────────────┐
                          │ Full consent participation│
                          │ n=909                    │
                          └─────────────────────────┘
┌──────────────────────┐      │
│ Ineligible after     │◄─────┤
│ consent       n=37   │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Eligible; Full consent   │
                          │ participation            │
                          │ n=872                    │
                          └─────────────────────────┘
┌──────────────────────┐      │
│ Deceased      n=1    │◄─────┤
│ Withdrawn     n=10   │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Given Baseline Q n=861   │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Deceased     n=16    │◄─────┼─────►│ Returned n=756 (88%) │
│ Withdrawn    n=6     │      │      └──────────────────────┘
│ Reduced MC   n=1     │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Sent 3m Q n=838          │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Deceased     n=13    │◄─────┼─────►│ Returned n=669 (80%) │
│ Withdrawn    n=37    │      │      └──────────────────────┘
│ Reduced MC   n=2     │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Sent 9m Q n=787          │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Deceased     n=20    │◄─────┼─────►│ Returned n=624 (79%) │
│ Withdrawn    n=26    │      │      └──────────────────────┘
│ Reduced MC   n=3     │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Sent 15m Q n=740         │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Deceased     n=16    │◄─────┼─────►│ Returned n=582 (79%) │
│ Withdrawn    n=25    │      │      └──────────────────────┘
│ Reduced MC   n=3     │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Sent 24m Q n=699         │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Deceased     n=38    │◄─────┼─────►│ Returned n=519 (74%) │
│ Withdrawn    n=47    │      │      └──────────────────────┘
│ Reduced MC   n=6     │      │
│ Admin error  n=3     │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Sent 36m Q n=608         │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Deceased     n=30    │◄─────┼─────►│ Returned n=439 (72%) │
│ Withdrawn    n=12    │      │      └──────────────────────┘
│ Reduced MC   n=5     │      │
│ Lost to F/U  n=1     │      │
│ Admin error  n=10    │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Sent 48m Q n=559         │
                          └─────────────────────────┘
┌──────────────────────┐      │      ┌──────────────────────┐
│ Deceased     n=29    │◄─────┼─────►│ Returned n=404 (72%) │
│ Withdrawn    n=9     │      │      └──────────────────────┘
│ Reduced MC   n=10    │      │
└──────────────────────┘      │
                          ┌─────────────────────────┐
                          │ Sent 60m Q n=526         │
                          └─────────────────────────┘
                              │      ┌──────────────────────┐
                              └─────►│ Returned n=371 (71%) │
                                     └──────────────────────┘
```