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ORIGINAL ARTICLE

The impact of chemotherapy on cognitive performance post-surgery in patients with colorectal cancer: A prospective cohort study

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Abstract

Objectives: Subjective reports of cognitive impairment following chemotherapy are frequent in cancer patients. Objective cognitive impairment has been observed in cancer patients regardless of treatment regimen suggesting the relationship between cognitive impairment and chemotherapy is not clear cut. Little research has explored the effects of chemotherapy on cognition following surgery in colorectal cancer (CRC). The present study explored the effects of chemotherapy on cognitive performance in a sample of CRC patients.

Methods: 136 participants were recruited into a prospective cohort study: 78 CRC patients undergoing surgery and adjuvant chemotherapy, 58 CRC patients undergoing surgery only. A battery of neuropsychological tests was administered to participants 4 weeks post-surgery (T1), 12 weeks after first chemotherapy (T2) and 3 months after last chemotherapy (T3) or equivalent time-points.

Results: Using the criterion of scoring at least two standard-deviations below the group norm on at least one neuropsychological test, 45%–55% of all CRC patients showed cognitive deficits 10 months after surgery (T3) and 14% on at least 3 tests. However, cognition did not significantly differ between patients who had chemotherapy and those who did not. A time by group interaction effect was found on the composite cognition score using multi-level modelling suggesting a greater improvement in cognition in the surgery only group over time ($p < 0.05$).

Conclusions: CRC patients display cognitive impairment 10 months after surgery. Chemotherapy did not worsen cognitive impairment but did appear to slow cognitive recovery relative to those undergoing surgery only. The findings demonstrate a clear need for supportive cognitive interventions for all CRC patients following treatment.

KEYWORDS
cancer, chemotherapy, cognition, colorectal, impairment, oncology, surgery

1 | INTRODUCTION

Colorectal cancer (CRC) average 5-year relative survival rates have increased from 22% to 57% in the United Kingdom over the last 40 years.[1] This reduction in mortality has led to an increased focus on quality of life. Cancer and its treatments can lead to a range of side effects, which negatively impact on patient quality of life. Impairment of cognitive function is one such side effect.[2]

The negative effects of surgery and anaesthesia on cognition have been demonstrated in CRC patients.[2,3] Adjuvant chemotherapy is routinely offered to CRC patients with high-risk stage II and stage III colorectal cancers to reduce the risk of local and systemic recurrence post-surgery in the United Kingdom.[4] Chemotherapy is ideally initiated 4–8 weeks after surgery, and its effects are likely to commence whilst some patients are still recovering from the cognitive effects of surgery and anaesthesia.

Several meta-analyses have confirmed the presence of objective cognitive deficits in patients undergoing chemotherapy across a range of cancers.[5,6] Whilst initially solely attributed to treatment with chemotherapy, hence the term 'chemobrain', it is becoming clear that a range of factors including the cancer, surgery, anaesthesia, fatigue and mood may play a role in the aetiology of cognitive impairment in cancer patients with some research indicating cognitive impairment present prior to systemic treatment.[5,7–11]

Research in CRC is limited with few longitudinal studies available to give accurate indications of the prevalence and incidence of cognitive impairment in CRC.[6] Existing studies suggests that CRC patients display greater cognitive impairment than matched healthy controls (43% vs 15%).[12] CRC patients exhibited impairment in attention/working memory, verbal learning/memory, and complex processing speed.[12] The relationship between chemotherapy and cognitive impairment in CRC remains unclear with research to-date presenting conflicting results, with some studies finding chemotherapy to be associated with poorer cognitive performance, but other studies finding no association.[5,12,13]

Despite the publication of international guidelines for researching cognitive impairment in cancer survivors,[14] a recent systematic review in colorectal cancer highlighted the need for future research to use standardised criteria and measures to define and assess cognitive impairment.[5] Furthermore, the review called for more research into the relationships between emotional distress and cognitive impairment to attempt to clarify these associations.[5]

The primary objective of the present research was to explore the impact of adjuvant chemotherapy on cognitive recovery post-surgery in CRC patients, adhering to International Cognition and Cancer Task Force (ICCTF) guidelines.[14] Specifically, comparing the frequency of cognitive deficits and changes in cognition over time between groups. It was hypothesised that recovery from post-surgery cognitive performance would be greater in patients who did not undergo adjuvant chemotherapy. The secondary objective was to explore the relationships between emotional distress, fatigue and cognition.

2 | MATERIALS AND METHODS

2.1 | Design

This study is reported in accordance with the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.[15] The data reported in this paper was taken from a prospective cohort study measuring cognition in two groups: (i) patients diagnosed with CRC who had undergone surgery 'surgery only group', (ii) patients diagnosed with CRC who had surgery followed by chemotherapy 'chemotherapy group'. A third group with no cancer history, 'learning control group', were recruited to control for learning effects on the neuropsychological tests only. Data was collected at three time-points:'T1' (approx. 4 weeks post-surgery, prior to chemotherapy), 'T2' (12 weeks after first scheduled chemotherapy [approx. 4 months post-surgery]), 'T3' (3 months after last scheduled chemotherapy for patients receiving 6 months of treatment or 6 months after last scheduled chemotherapy for patients receiving 3 months of treatment (approx. 10 months post-surgery)). Data was collected from the surgery group at equivalent time-points.

2.2 | Procedure

A consecutive series of outpatients attending oncology clinics from five London Hospitals were invited to participate in the study between April 2014 and July 2018. Inclusion criteria: aged 18 years and over; diagnosed with resectable CRC to be followed by adjuvant chemotherapy treatment (chemotherapy group) or no further systemic cancer treatment (surgery group); fluent in spoken and written English sufficient to complete the assessments (based on clinician and/or researcher observations). Exclusion criteria: prior exposure to chemotherapy; significant comorbidities which could affect ability to participate; history of stroke or other brain trauma. All exclusion criteria were identified through medical records or self-report. Eligible patients were identified and approached by a member of the research team at each Hospital. Those interested in participating were contacted by a research assistant by telephone. Participants were contacted by telephone to arrange all subsequent follow-up appointments.

Healthy adult volunteers aged 18 years and over with fluent written and spoken English were recruited from communities within hospital catchment areas.

Assessments were conducted in a private room in the hospital, the University or at the participant's home. All participants provided

written, informed consent. Ethical approval for the study was granted by South West–Cornwall and Plymouth National Health Service Research Ethics Committee (Ref:13/SW/0201).

2.3 | Assessments

Demographic and clinical information were collected at T1. A battery of neuropsychological assessments (NP) was used to assess cognitive function at all three time-points conducted by a trained research assistant. Initial assessment took place in clinic with follow up assessments conducted at the participants home. The battery included the three core measures recommended by the ICCTF[14]: the Trail Making Test (TMT A&B),[16] a test of attention, executive function and visuomotor ability; Hopkins Verbal Learning Test–Revised,[17] a test of verbal memory (immediate and delayed recall, retention and recognition); the Controlled Oral Word Association Test (COWA, phonemic and semantic versions), a test of verbal fluency and executive function.[18] These were supplemented with the Digit Span subtest of the Wechsler Adult Intelligence Scales–Third Edition, (WAIS-III Digit Span), a test of attention and working memory[19]; The Symbol Digit Modalities Test (SDMT, written and oral versions),[20] a test of attention, visuo-motor ability and concentration; Grooved Pegboard Test (GP, dominant and non-dominant hand), test of fine motor function[21] and The Benton Visual Retention Test, a test of immediate recall visual memory (number correct and number of errors recorded).[22] Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale[23] and fatigue using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F v4).[24] Further details of the methodology can be found in the study protocol.[25]

A number of steps were taken to minimise potential bias in the study. Both the methods and analyses strictly adhered to the ICCTF guidelines. Standardised neuropsychological tests were administered by trained researchers and alternate forms were used when possible. Tests scores were normed for age and gender and the effects of age, cancer stage and education were controlled in the analyses. The effects of learning were controlled for using data from a learning control group where appropriate. Multiple methods of analysis were used, drop-outs were adjusted for through the use of multilevel modelling, and multiple imputation was used to account for missing data at each time point.

2.4 | Sample size

A sample size calculation was performed using GPower3.1. To detect an effect size of−0.26 with 80% power and a significance level of 0.05 at the final time point, a minimum sample size of 120 participants was indicated. Based on medium effect sizes in a meta-analysis of chemotherapy and cognitive function,[2] a sample size of 120 would allow effects to be detected in the following domains: executive function, information processing speed, language, motor function, verbal memory and visual memory. However, it is acknowledged small effects may not be detected in the following domains: attention and visuospatial skills. Assuming an overall attrition rate of 22% (based on SCOT trial [Short Course Oncology Treatment - A Study of Adjuvant Chemotherapy in Colorectal Cancer] attrition rates[1 26]), a total sample size of 156 participants was sought.

A total of 136 participants were recruited into the study: 78 in the chemotherapy group, 58 in the surgery only group. A breakdown of recruitment is given in the flow chart (Figure 1).

3 | STATISTICAL ANALYSES

Analysis of missing data among all variables of the study was undertaken. Initial analyses determined participants lost to follow-up as a percentage, per group. Thereafter missing data levels per timepoint were ascertained. If missing value levels were >5% per variable at any timepoint, missing values within a timepoint were multiply imputed ($m = 10$) for each timepoint individually, using available data from all timepoints within the imputation model. Imputation was conducted with the Statistical Product and Service Solutions (IBM-SPSS) Multiple Imputation function using the Markov Chain Monte Carlo Linear algorithm, and limits for maximum and minimum values based on available data. Ten imputations were generated ($m = 10$). Each dataset was used in analyses independently, and thereafter the results of the 10 analyses were combined in the final stage of multiple imputation procedures outlined by Rubin[27]; Shaefer and Olsen[28] and Allision.[29] Analyses where adjustments were made for learning effects (see below) were done on a per imputation basis.

Raw scores on each neuropsychological test, for each participant, were standardised by taking the normative population mean score for each test[18,20,30–34] from participant mean scores and dividing by the population standard deviation (from the same source). Where higher scores were indicative of poorer performance, these scores were reversed so higher standardised scores represented better performance across all tests. Negative standardised scores indicate performance below the population mean and positive scores indicate performance above the population mean.

Composite NP scores for each participant were calculated by taking the mean z-score across 14 tests (the COWA semantic version was not a standardised score therefore excluded), at each timepoint. The mean score across tests rather than a sum was used to retain the original metrics of the standardised scores.

In line with the ICCTF recommendations on reporting analyses based on individual tests scores[14] multiple methods were used to assess change in cognitive performance over time.

3.1 | Calculating the number of scores in deficit/ number of ppt considered in deficit

Two deficit scores (0 = not in deficit; 1 = in deficit) were calculated for each neuropsychological test score; 1.5 SD and 2 SD below the group mean score. The total number of tests in deficit (at a timepoint) for each was calculated for each participant to determine if they were in cognitive impairment as follows. Ingraham and Aiken[35] provide useful data on determining criteria for impairment in multiple test batteries.

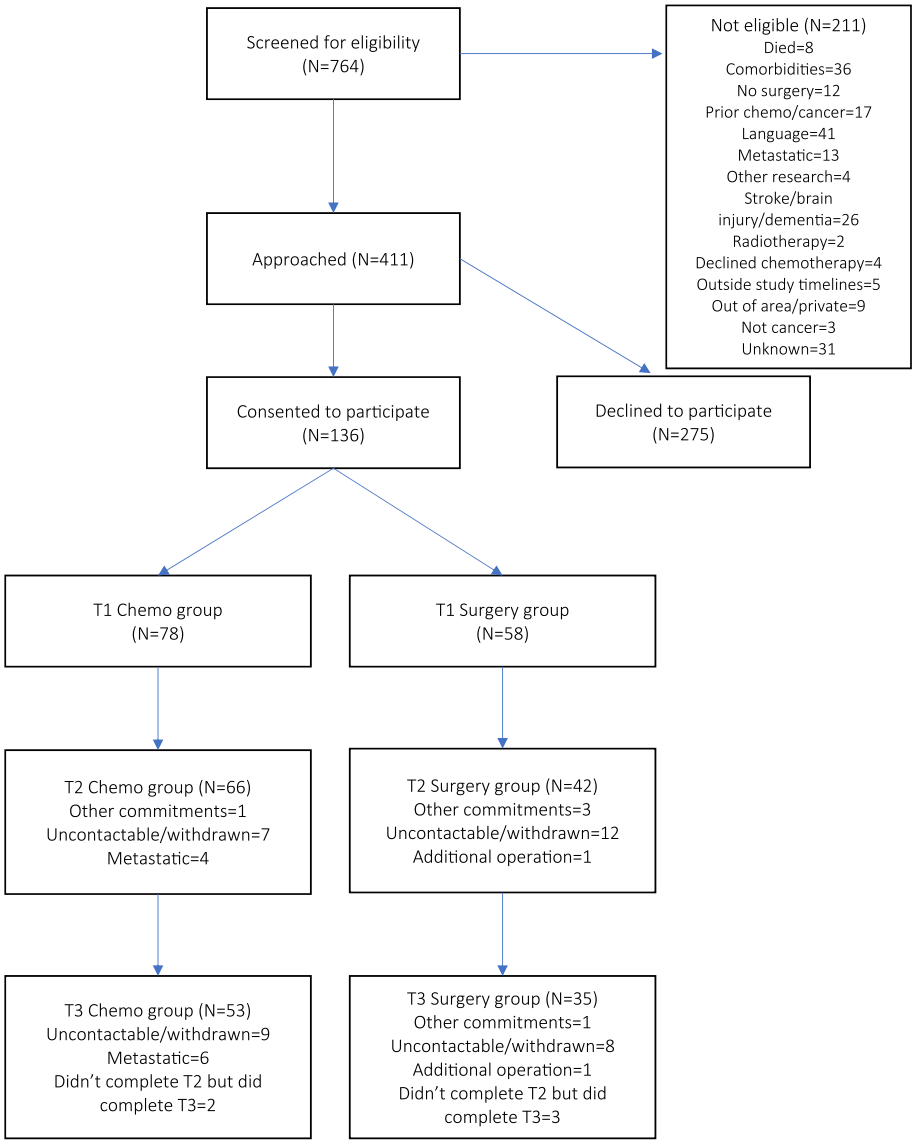


FIGURE 1 Patient recruitment flowchart.

The present study yielded 15 scores from seven neuropsychological tests. On the basis of 15 tests, when employing the criteria of 2SD below the mean, according to the Ingraham and Aiken[35] criteria 30% of the population would be expected to score at least 2SD below the mean on one test out of 15% and 1% of the population would be expected to score 2SD below the mean on at least 3 tests.

3.2 | Learning adjusted difference scores (AdjΔ) between timepoints (AdjΔT1T2 and AdjΔT1T3)

For each participant the difference in each test score at follow-up, from the baseline scores was calculated by subtracting baseline z-scores from follow-up z-scores. To generate learning adjusted difference scores (AdjΔT1T2 and AdjΔT1T3), the mean change in the learning control group (representative of natural learning over multiple testing) was subtracted from the individual difference scores of the chemotherapy and surgery participant scores.

3.3 | Residualised change scores

Z-scores for each NP test and composite score were utilised to generate Residualised change scores (RCS) (for each participant), by saving the standardised residuals after predicting follow-up scores from baseline scores using simple linear regression. Independent linear regressions were run for each treatment group (chemotherapy and surgery) and were done for T2 and T3 separately.

3.4 | Reliable change Index (RCI)

The RCI for each NP test was computed utilising Hsu[36] method. As with the RCS, this was calculated per treatment group using treatment group-based means, standard deviation and test-retest correlations; and were done for T2 and T3 separately.

Standardised scores (transformed for each NP test), number of tests in deficit, and change scores between timepoints (i.e. learning adjusted difference scores, RCS and RCI between T1 and T2, and T1 and T3) were utilised to perform analyses between groups and over time.

Chi-square (Fisher's exact) tests were used to identify significant differences in the proportion of participants in each group showing a deficit of at least 1.5SD on at least two tests or 2SD on one test at all three timepoints. For group differences in NP indices, continuous measures were examined using *t*-tests (corrected for heterogeneity of variance where necessary). Thereafter, a series of multiply imputed regression analyses were performed to test for group differences (controlling for age, education, and cancer stage) on each of the 15 individual cognitive test scores and the composite score, for standardised scores (at T1,T2andT3) and for the learning adjusted difference scores, the RCS and the RCI scores for test performance between T1 and T2, and separately for performance between T1 and T3. Finally, to examine changes in each NP score over time by group, a series of multi-level models (MLM) were conducting, using group (surgery plus chemotherapy vs. surgery only) and time (T1vsT2vsT3) as main effects and a time by group interaction, also controlling for effects of age, education, cancer stage. Significant effects were explored within effect and across the interaction using post hoc tests on adjusted means ($p < 0.05$ for significance).

4 | RESULTS

Participant characteristics are shown in Table 1. The surgery only group were significantly older than the chemotherapy group. The majority of the chemotherapy group had stage III cancer compared to stage II in the surgery only group. The average number of days to follow-up were 94 from T1 to T2 and 181 from T2 to T3. The group ($N = 55$) recruited to control for learning effects on neuropsychological tests overtime had a mean age of 57.8 years and 60% were female. Z-scores for each neuropsychological test are available in the Supplementary Material (Table S1).

4.1 | Primary objective

4.1.1 | Cognitive domains affected

Deficits, defined as two standard deviations (2SD) below the mean performance, were seen across a broad range of neuropsychological tests. The greatest proportion deficits occurred in motor function (42% of cancer patients), verbal learning (19% cancer patients), and verbal fluency (14%). A similar pattern was observed when using the 1.5 SD criterion.

4.1.2 | Frequency of cognitive deficits by group

The graph below (Figure 2.) shows the percentage of participants in each cancer group scoring at least two SD below the mean score on at least one test and at least three tests at each timepoint compared to the proportions expected in a normal population due to chance alone.[35] Perceptuo-motor (42% scored 2SD below the mean), memory (19% at 2SD) and executive function (16% at 2SD) were the cognitive domains most frequently affected.

At all timepoints both groups showed a greater percentage of participants with deficits on both one and three tests than would be expected by chance in the normal population. A similar pattern was observed when using the 1.5SD criterion.

Visual inspection suggests that by T3 the proportion of patients showing impaired performance on either criterion had decreased.

Chi-squared tests computed to identify significant differences in the proportion of participants in each group showing a deficit showed no significant group differences at any timepoint (Supplementary Table S9). No group differences in change in neuropsychological test scores were found at any timepoints using learning adjusted change scores, RCI, and RCS (Supplementary Tables S2a-c to S8).

4.1.3 | Change in cognitive performance over time

Supplementary Table S10 presents the results of an MLM exploring changes in neuropsychological test performance in each group over time controlling for age, education and cancer stage. Of particular note is the time by group interaction effect significant at the $p < 0.05$ level for the composite neuropsychological test score. Post-hoc tests showed that the groups did not significantly differ within each timepoint ($p > 0.05$); however, while the chemotherapy group did not show significant differences between T1, T2 or T3 in pairwise comparisons ($p > 0.05$), the surgery only group showed significant increases in scores between T1 and T3 ($p = 0.017$) and T2 and T3 ($p < 0.001$). This suggests that the surgery only group showed an improvement in test performance over time, while the chemotherapy group showed no improvement (See Figure 3).

4.2 | Secondary objective

4.2.1 | Cognition, mood and fatigue

Pearson's correlations were performed between composite neuropsychological score and depression, anxiety and fatigue at all time points. The relationship between mood, fatigue and cognition was not strong, with weak correlations found between fatigue and cognition

TABLE 1 Participant characteristics by group at baseline assessment.

	Total (95% CI) *(%)* *N* = 136	Chemotherapy group (95% CI) *(%)* *N* = 78	Surgery group (95% CI) *(%)* *N* = 58	Group differences *t*/chi *(p* value*)*
Characteristic				
Gender	191	78	58	
Men	91 *(47.6)*	41 *(52.6)*	28 *(48.3)*	
Women	100 *(52.4)*	37 *(47.4)*	30 *(51.7)*	$\chi^2 = 0.245$ *(p = 0.621)*
Age	61.3 *(59.5, 63.2)*	60.2 *(57.5, 63.0)*	66.1 *(62.9, 69.3)*	*t = 2.595 (p = 0.004)*
Highest level of education attained				
Primary	1 *(0.5)*	0	0	
Secondary—lower	33 *(17.2)*	13 *(16.7)*	14 *(24.1)*	
Secondary—higher (16+)	29 *(15.2)*	16 *(20.5)*	8 *(13.8)*	
Higher education—cert/dip	44 *(23)*	21 *(26.9)*	16 *(27.6)*	
Degree	55 *(28.8)*	15 *(19.2)*	16 *(27.6)*	
Masters	23 *(12.0)*	9 *(11.5)*	3 *(5.2)*	
Doctoral	6 *(3.1)*	4 *(5.1)*	1 *(1.7)*	$\chi^2 = 5.387$ *(p = 0.371)*
Tumour stage (frequency)				
Stage I	16 *(12.0)*	2 *(2.9)*	14 *(24.1)*	
Stage II	57 *(41.8)*	19 *(24.6)*	38 *(64.8)*	$\chi^2 = 53.350$ *(p < 0.0001)*
Stage III	62 *(45.3)*	56 *(71.2)*	6 *(10.5)*	
Stage IV	1 *(1.0)*	1 *(1.3)*	0 *(0.5)*	
Chemotherapy regimen *(%)*				
FOLFOX/OxMdG (folinic acid + fluorouracil + Oxaliplatin)	NA	24 *(32)*	NA	
Xelox/CapOx (Oxaliplatin + capecitabine)	NA	25 *(34)*	NA	
Xeloda (capecitabine)	NA	12 *(16)*	NA	
5FU/de gramont or modified de gramont: Fluorouracil	NA	13 *(18)*	NA	
Marital status				
Never married	27 *(14.1)*	12 *(15.4)*	10 *(17.2)*	
Married/Civil partnership/Cohabiting	123 *(64.4)*	49 *(62.8)*	29 *(50)*	
Separated, divorced, or formerly in civil partnership	25 *(13.1)*	12 *(15.4)*	10 *(17.2)*	$\chi^2 = 3.775$ *(p = 0.287)*
Widowed or surviving partner from civil partnership	16 *(0.4)*	5 *(6.4)*	9 *(15.5)*	
Number of comorbidities				
0	67 *(35.1)*	22 *(28.2)*	20 *(34.5)*	
1	58 *(30.4)*	23 *(29.5)*	19 *(32.6)*	
2	36 *(18.8)*	15 *(19.2)*	12 *(20.7)*	$\chi^2 = 2.853$ *(p = 0.583)*
3	15 *(7.9)*	9 *(11.5)*	4 *(6.9)*	
4	14 *(7.3)*	9 *(11.5)*	3 *(5.2)*	
7	1 *(0.5)*	0	0	

TABLE 1 (Continued)

	Mean (standard deviation) T1 *N* = 136 Total	Mean (standard deviation) T1 *N* = 78 Chemotherapy group	Mean (standard deviation) T1 *N* = 58 Surgery group	Group differences *t*/chi (*p* value)
HADS-Depression T1	4.30 (*3.52*)	4.28 (*3.33*)	4.33 (*3.78*)	*t* = 0.074 (*p* = 0.941)
HADS-Anxiety T1	6.05 (*4.31*)	6.18 (*4.31*)	5.88 (*4.35*)	*t* = −0.400, (*p* = 0.690)
FACT-Fatigue T1	36.55 (*11.27*)	36.10 (*11.356*)	37.15 (*1.21*)	*t* = 0.536, (*p* = 0.593)
	Mean (standard deviation) T2 *N* = 108 Total	**Mean (standard deviation) T2 *N* = 66 Chemotherapy group**	**Mean (standard deviation) T2 *N* = 42 Surgery group**	**Group differences *t*/chi (*p* value)**
HADS-Depression T2	3.85 (*2.87*)	5.09 (*2.12*)	2.95 (*2.63*)	*t* = −3.823 (*p* < 0.001)
HADS-Anxiety T2	5.37 (*3.551*)	5.39 (*3.95*)	5.10 (*3.67*)	*t* = −0.390 (*p* = 0.349)
FACT-Fatigue T2	37.42 (*11.15*)	30.92 (*11.17*)	41.35 (*9.95*)	*t* = 4.888 (*p* < 0.001)
	Mean (standard deviation) T3 *N* = 88 Total	**Mean (standard deviation) T3 *N* = 53 Chemotherapy group**	**Mean (standard deviation) T3 *N* = 35 Surgery group**	**Group differences *t*/chi (*p* value)**
HADS-Depression T3	3.53 (*3.04*)	4.22 (*3.06*)	3.37 (*3.24*)	*t* = −1.214 (*p* = 0.117)
HADS-Anxiety T3	5.22 (*3.89*)	5.68 (*4.36*)	4.37 (*3.61*)	*t* = −1.444 (*p* = 0.076)
FACT-Fatigue T3	39.93 (*11.56*)	36.74 (*13.54*)	41.38 (*10.23*)	*t* = 1.695 (*p* = 0.47)

Note: T1—approx. 4 weeks post-surgery, prior to chemotherapy. T2—12 weeks after first scheduled chemotherapy (approx. 4 months post-surgery). T3—3 months after last scheduled chemotherapy for patients receiving 6 months of treatment or 6 months after last scheduled chemotherapy for patients receiving 3 months of treatment (approx. 10 months post-surgery). t = t-value and X^2 = chi square statistic.

Abbreviations: FACT, Functional Assessment of Cancer Therapy – Fatigue; HADS, Hospital Anxiety and Depression Scale.

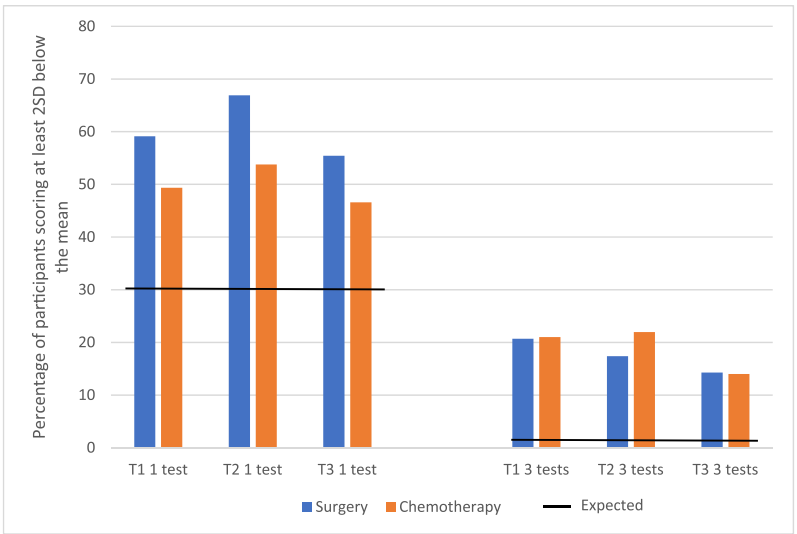
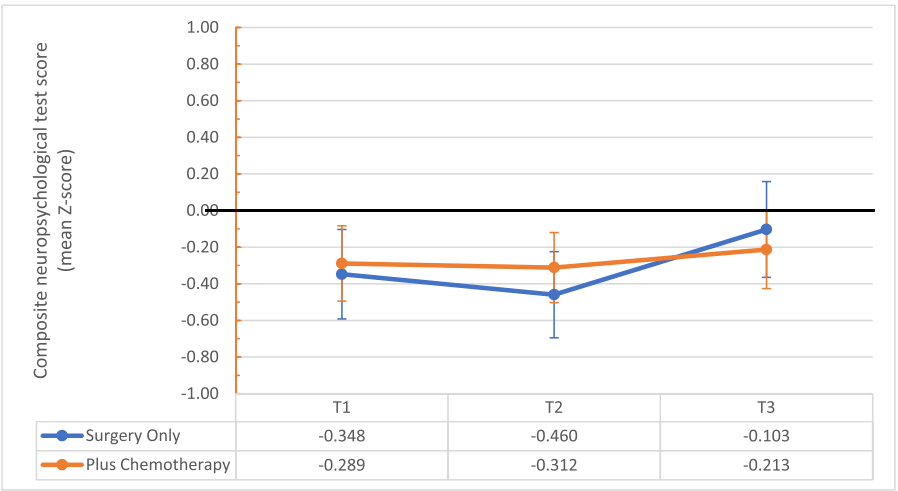


FIGURE 2 Percentage of participants in each group scoring at least 2 standard deviations below the mean on at least one and at least three neuropsychological tests at each timepoint shown with the expected percentage in a normal population.

SD=standard deviation, Expected=percentage of the general population expected to score at least 2SD below the mean(Ingraham & Aiken,1996)
T1 - approx. 4 weeks post-surgery, prior to chemotherapy (Chemotherapy group N=78, Surgery group N=58)
T2 - twelve weeks after first scheduled chemotherapy (approx. 4 months post-surgery) (Chemotherapy group N=66, Surgery group N=42)
T3 - three months after last scheduled chemotherapy for patients receiving six months of treatment or six months after last scheduled chemotherapy for patients receiving three months of treatment (approx. 10 months post-surgery) (Chemotherapy group N=53, surgery group N=35)



T1 - approx. 4 weeks post-surgery, prior to chemotherapy (Chemotherapy group N=78, Surgery group N=58)
T2 - twelve weeks after first scheduled chemotherapy (approx. 4 months post-surgery) (Chemotherapy group N=66, Surgery group N=42)
T3 - three months after last scheduled chemotherapy for patients receiving six months of treatment or six months after last scheduled chemotherapy for patients receiving three months of treatment (approx. 10 months post-surgery) (Chemotherapy group N=53, surgery group N=35)

FIGURE 3 Composite neuropsychological test score over time by group.

at T2 ($r = 0.183$, $p < 0.023$) and T3 ($r = 0.238$, $p = 0.010$). Greater depression was correlated with poorer cognition at T3 (−0.273, $p = 0.003$) only. This pattern was repeated in individual group analyses. Between group analyses of depression, anxiety and fatigue revealed that the chemotherapy group experienced significantly more depression and fatigue at T2 than the surgery only group (Table 1). Depression ($F_{[2]} = 3.339$, $p = 0.040$) and fatigue ($F_{[2]} = 7.676$, $p < 0.001$) were found to significantly worsen at T2 in the chemotherapy group. No other differences in anxiety, depression and fatigue overtime were found in either group.

5 | DISCUSSION

The present study examined the impact of chemotherapy on cognitive recovery post-surgery in CRC patients by comparing those who received chemotherapy after surgery and those who did not. The proportion of cancer patients in both groups demonstrated much higher deficits in cognitive function than would be expected in the normal population. The proportion with impaired scores (one test at 2SD) was similar to those found in previous CRC research (47%–67%).[12]

Although both groups demonstrated deficits in cognitive function there were no differences in cognitive performance between groups at any timepoints consistent with previous research in breast cancer.[10] However, the MLM analysis found that the surgery only group, despite being older, showed a greater improvement in overall cognitive performance over time than the chemotherapy group. This finding suggests that while the observed cognitive deficits in both groups are likely attributable to the effects of surgery, and/or the cancer itself[11] the addition of chemotherapy may slow post-surgical cognitive recovery.

This dual impact of surgery and chemotherapy may explain the inconsistent research findings regarding the effect of chemotherapy on cognition to date.[5] Research has shown no effect of chemotherapy on cognition[12] and poorer cognition in CRC patients having chemotherapy.[13] A larger sample assessed over a longer time frame is required to tease out the effects of chemotherapy and surgery and the potential role of some other element of the cancer process.

Consistent with prior research[12] there was little association between mood, fatigue and cognition supporting the assertion that the observed deficits were attributable to surgery. The chemotherapy group showed greater depression and fatigue than the surgery only group during chemotherapy, but these differences reduced post chemotherapy.

The results indicate that interventions aimed at supporting patients and reducing the impact of cognitive deficits should not be limited to those undergoing chemotherapy.[37]

5.1 | Study limitations

While the use of a consecutive series of patients from multiple sites allows these findings to be generalised to the wider CRC population, the study is not without limitations. These include the small sample size and expected loss to follow-up. Recruitment was challenging, patients were approached whilst recovering from surgery and a large proportion declined to participate (59%). This may have caused sampling biases and limited the statistical power to detect differences between the patient groups. Baseline assessment took place in clinic with subsequent assessments at the participants home. The potential impact of context specific learning should be considered.[38] It was not possible to analyse different treatment regimens on cognitive performance, as these were too varied and any analyses would have limited statistical power. A substantial loss of follow-up was found (up to 40%) with many participants reporting wanting to

move forward with life, deteriorating health, complications, multiple healthcare appointments, and return to work and usual routine acting as barriers to participation. However, the use of covariates and MLM in the statistical analysis increased the power and partially mitigated the reduced sample size.

Despite these limitations this paper reports one of the few longitudinal studies of cognitive impairment in patients with CRC whilst controlling for learning effects and including a pre-chemotherapy cognitive function baseline. The study closely adhered to the ICCTF guidelines for both assessment and analysis, increasing the robustness of the findings and allowing cross-study comparison.

5.2 | Clinical implications

CRC patients undergoing surgery, regardless of chemotherapy status, should be monitored for cognitive difficulties and support and appropriate referral made for those with impairment which impacts their daily functioning.

6 | CONCLUSIONS

This study confirms the presence of objective cognitive impairment up to 10 months after surgery in people with CRC. Those not undergoing chemotherapy showed greater recovery over time. Further follow-up of this cohort will enable a better understanding of the long-term trajectory of cognitive impairment following surgery for CRC. There is now adequate evidence to suggest the need for supportive cognitive interventions for those undergoing treatment for CRC.

AUTHOR CONTRIBUTIONS

Marie-Rose Dwek contributed to the design of the study, data collection and drafted the manuscript. Stanton P. Newman contributed to the design of the study, analysis of the data and drafted the manuscript. Stefano Brini contributed to analysis of the data and reviewed the manuscript. Pru Holder contributed to data collection and reviewed the manuscript. Michael Machesney contributed to the design and conduct of the study and reviewed the manuscript. David Propper contributed to the design and conduct of the study and reviewed the manuscript. Lorna R. Rixon contributed to the design of the study, data collection and reviewed the manuscript. Shashivadan P. Hirani contributed to the design of the study, analysis of the data and drafted the manuscript. Catherine S. Hurt contributed to the design of the study, analysis of the data and drafted the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval for the study was granted by South West–Cornwall and Plymouth NHS Research Ethics Committee (Ref: 13/SW/0201).

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ENDNOTE

[1] Personal communication with Dr Bridgewater of University College London Hospital.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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