Effects of Adjuvant Chemotherapy on Cognitive Function of Patients With Early-stage Colorectal Cancer

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Abstract

Cognitive dysfunction can occur after chemotherapy in cancer survivors but has not been widely investigated in colorectal cancer (CRC). Among patients with stage II or III CRC who had been prospectively assessed for neuropsychological function and had completed cognitive complaint questionnaires, those who had received fluoropyrimidine-based adjuvant chemotherapy presented with declines in executive function after 12 months compared with those patients who had not received chemotherapy.

Purpose: Chemotherapy-related cognitive impairment can occur in cancer survivors after treatment, especially those patients who have undergone chemotherapy for breast cancer. The frequency and to what extent such toxicity develops in colorectal cancer (CRC) survivors is unknown. The present prospective study evaluated the effects of adjuvant chemotherapy on the cognitive performance of patients with localized CRC compared with a control group who had not undergone chemotherapy. **Patients and Methods:** Consecutive patients with localized stage II and III CRC completed neuropsychological assessments, self-reported cognitive complaint questionnaires, and depressive symptom evaluations before starting fluoropyrimidine-based adjuvant chemotherapy and after 12 months. Blood was collected for apolipoprotein E genotyping. Diffusion tensor imaging data were acquired from a subset of participants at both evaluation points. **Results:** From December 2012 to December 2014, 137 patients were approached and 85 were included. Of these 85 patients, 49 had undergone chemotherapy and 26 had not, in accordance with the standard recommendations for adjuvant therapy for CRC. The mean age was 62.5 ± 9.4 years, 60% were men, and the mean educational attainment was 7.6 ± 3.7 years. No difference was found in the global composite score ($P = .38$), attention ($P = .84$), or memory ($P = .97$) between the 2 groups during the follow-up period (mean ± standard deviation, 375 ± 29 days). However, a statistically significant difference was found for executive function after adjustment for age, sex, education, and depressive symptoms at baseline (β −1.80; 95% confidence interval, −3.50 to −0.11; $P = .04$), suggesting worse performance for the chemotherapy group. For the 32 patients who had undergone magnetic resonance imaging, tract-based spatial statistics did not show voxelwise significant differences in structural brain connectivity at baseline or during follow-up. Apolipoprotein E polymorphisms were not predictive of cognitive dysfunction. **Conclusion:** Patients with CRC who received adjuvant 5-fluorouracil with or without oxaliplatin presented with a decline in executive function after 12 months compared with patients with localized disease who had not received chemotherapy.

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Introduction

More than 30 years ago, cancer survivors started describing cognitive complaints after receiving chemotherapy, which they termed "chemobrain" in support groups.[1] Since then, increasing evidence from longitudinal studies has supported that cytotoxic drugs given systemically for non–central nervous system tumors might lead to cognitive adverse effects.[2-29] According to the results from several meta-analyses, chemotherapy can be related to mild to moderate cognitive impairment in many domains, including attention, processing speed, executive function, and verbal and visual memory.[30-34] These changes suggest a pattern of lesions to frontal-subcortical white matter (WM) networks, which was confirmed by alterations in brain structure and function reported by previous neuroimaging studies.[28,35]

However, most of the evidence of chemotherapy-related cognitive impairment (CRCI) has come from trials of breast cancer survivors. Only 2 longitudinal studies have evaluated the effects of adjuvant chemotherapy for colorectal cancer (CRC) on cognitive function.[36,37] The results were conflicting, with an uncontrolled small prospective trial of 57 patients showing no cognitive decline 6 months after chemotherapy,[37] and a large and controlled study of 289 patients demonstrating that patients with CRC had greater cognitive impairment than healthy controls at diagnosis and after 12 months of follow-up, although without a significant added effect from chemotherapy.[36]

In addition, experimental research has demonstrated that chemotherapeutic agents, such as 5-fluorouracil, cause extensive damage to myelin,[38] which is the hallmark of WM tracts. Diffusion tensor imaging (DTI) takes advantage of the intrinsic property of anisotropic water diffusion in neural tissues to noninvasively probe WM microstructural integrity. A recent study indicated significant decreases of fractional anisotropy (FA) in frontal, parietal, and occipital WM tracts in a group of 34 chemotherapy-exposed breast cancer patients (3-5 months after treatment) compared with 19 healthy controls and 16 breast cancer patients without exposure to chemotherapy, with significant correlations of FA and neuropsychological performance decline in the domains of attention and verbal memory.[28] To the best of our knowledge, to date, no other longitudinal DTI studies of WM chemotherapy-induced changes have been performed for CRC patients.

The apolipoprotein E (APOE) E4 allele has been associated with various disorders with prominent cognitive dysfunction, including an increased risk of Alzheimer's disease, and worse outcomes after stroke and traumatic brain injuries.[39,40] It has also been associated with poorer cognitive performance in cancer survivors in some studies,[41] although not in others.[36]

The aim of the present study was to evaluate the effect of adjuvant chemotherapy, a combination of 5-fluorouracil and leucovorin with or without oxaliplatin, on the cognitive function of patients with localized CRC compared with a control group with localized CRC who had not undergone chemotherapy at baseline and after 12 months. As a secondary aim, we investigated the brain WM molecular properties using DTI in a subset of individuals and evaluated the predictive roles of apolipoprotein polymorphisms on CRCI.

Patients and Methods

Participants

Patients with localized CRC were consecutively recruited at their first appointment with the oncologist at a large public academic cancer center in São Paulo, Brazil. The inclusion criteria for the chemotherapy group (CTh^+) were high-risk stage II and stage III CRC with the recommendation to start 6 cycles (6 months) of 5-fluorouracil and leucovorin with or without oxaliplatin. The inclusion criteria for the control group were stage II low-risk CRC without an adjuvant chemotherapy (CTh^-) indication. Participants were excluded if they had had a previous malignancy, had metastatic disease, had a history of any neurologic condition that could impair cognitive function (eg, dementia, stroke, brain injury), had depression, or had had < 4 years of education (which could impair their performance on the neuropsychological evaluation). Cancer progression or recurrence resulted in withdrawal from the study because the patients would require different chemotherapy protocols. The local research ethics board approved the present study, and all eligible patients provided written informed consent before enrollment.

Study Design

The present observational prospective controlled study analyzed the cognitive performance of patients with early-stage CRC with and without chemotherapy during a 12-month period. The baseline assessment was performed 1 to 3 months after surgery and before the start of adjuvant therapy (t1). Adjuvant chemotherapy was planned for 6 months. The follow-up assessment for the CTh^+ patients was conducted 12 months after chemotherapy initiation (t2). The control group (CTh^-) was evaluated at matched intervals. A subgroup of patients and controls underwent brain magnetic resonance imaging (MRI) at t1 and t2 to evaluate the structural and functional alterations.

Assessments

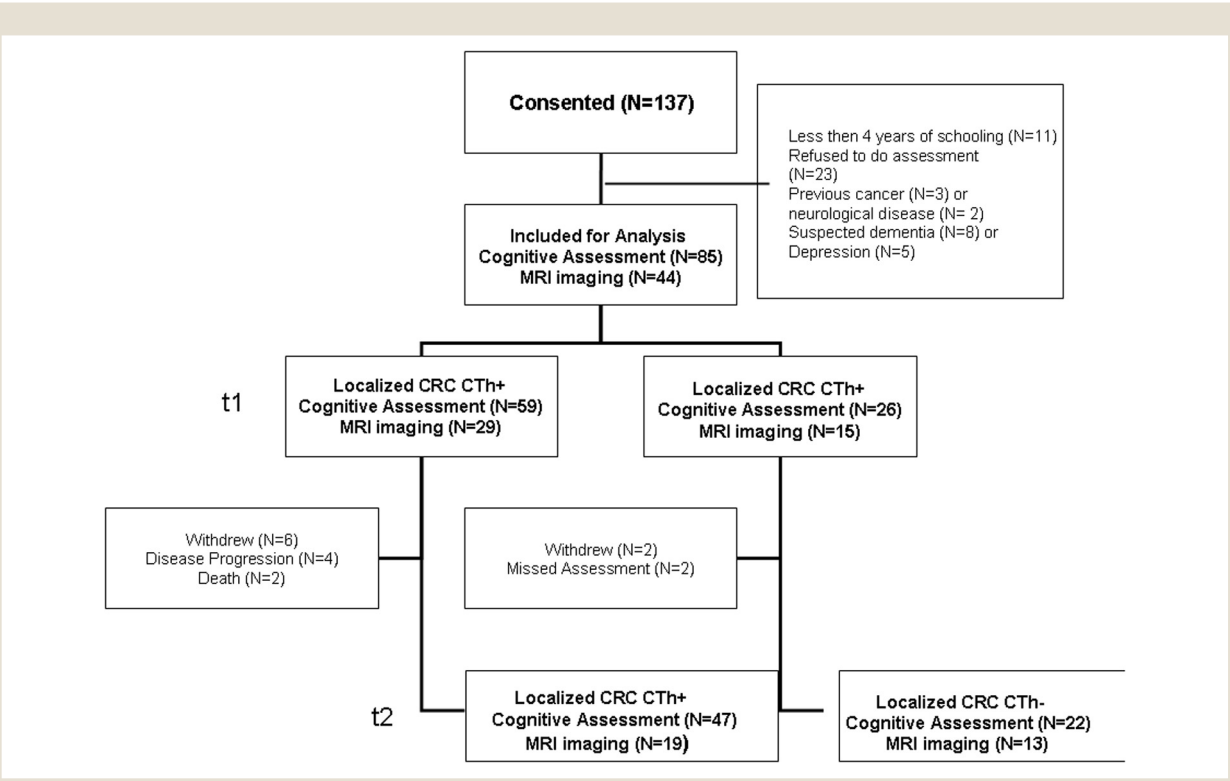
At baseline, cognitive function was measured using a battery of 13 neuropsychological tests that included specific cognitive domains: verbal and visual memory, attention, visuospatial, and executive function (Table 1).[42] The neuropsychological assessment was conducted by a neuropsychologist or a skilled geriatrician who were unaware of the participants' chemotherapy status. All evaluations were performed in a silent room without interruptions. The time required for completion was, on average, 90 minutes.

All patients were screened for dementia using the Mini-Mental State Evaluation[43] and the Functional Activities Questionnaire.[44] Patients with poor performance on the Mini-Mental State Evaluation (score < 24) and Functional Activities Questionnaire (score > 4) were excluded from the present study. The presence of depressive symptoms was evaluated using the Patient Health Questionnaire,[45] and those

Table 1 Cognitive Domains and Related Neuropsychological Tests

Domain	Test
Memory	Hopkins verbal learning test[42]; Brief visuospatial memory test[42]
Attention	Digit span-forward[42]; Trail making test, part A[42]; Digit-symbol[42]
Executive Function	Digit span-backward[42]; Semantic verbal fluency (animals)[42]; Trail making test, part B[42]; Stroop C[42]; Phonemic verbal fluency[42]

Figure 1 CONSORT (Consolidated Standards of Reporting Trials) Flow Diagram



Abbreviations: CTh^+ = chemotherapy exposed; CTh^- = had not received chemotherapy; CRC = colorectal cancer; MRI = magnetic resonance imaging; t1 = baseline assessment; t2 = assessment 12 months after chemotherapy initiation.

participants with a score $\geq$ 12 were excluded. Those who fulfilled the criteria for a major depressive disorder were excluded and referred for psychiatric evaluation. Self-reported cognitive complaints were assessed using the Everyday Cognition questionnaire.[46] The comorbidity burden was graded using the Charlson comorbidity index.[47]

Blood samples were collected for APOE genotyping.[48] APOE alleles were identified using polymerase chain reaction technique with the Taqman SNP Genotyping assay (Applied Biosystems, Foster City, CA).

Imaging Acquisition

Patients underwent imaging on a 3T scanner (Discovery MR750; GE Healthcare, Waukesha, WI) using an 8-channel head coil. The DTI protocol included an axial single-shot, echo planar-based sequence with 32 encoding directions with b = 0 and 1000 s/mm^2 and the following parameters: repetition time/echo time, 9500/82.2 ms; spatial resolution, 1 × 1 (in plane) × 2.9 mm (slice thickness); matrix size, 128 × 128; and field of view, 256 × 256 mm^2. Whole brain coverage was obtained with 77 slices, and the duration for the DTI scan was 8 minutes. Structural images were also acquired to evaluate incidental findings and consisted of sagittal 3-dimensional T1-weighted fast-field echo and fluid attenuation inversion recovery sequences, both with 1-mm isotropic voxels.

DTI Processing and Analyses

DTI data were processed using the functional MRI brain software library (FSL), version 5.0.10.[49] Brain extraction was performed using the FSL brain extraction tool.[50] Head motion and eddy current artifacts were corrected using the Eddy tool.[51] The diffusion tensor model was fitted to the resulting images to produce maps of FA, mean diffusivity, axial diffusivity, and radial diffusivity in individual subjects.

Voxelwise analyses were assessed using tract-based spatial statistics.[52] All registered FA maps for both groups were aligned into the Montreal Neurological Institute 152 space using the FSL nonlinear registration tool.[53-55] The mean FA image was subsequently created and thinned using a threshold FA $>$ 0.2 to create a mean FA skeleton, which represents the centers of WM tracts common to the entire group. Voxelwise differences were then assessed using general linear modeling and a randomize algorithm,[56] with 5000 permutations and threshold-free cluster enhancement.[57] Clusters with $>$ 200 voxels with a significant family-wise error-corrected $P < .05$ were considered statistically significant.

Statistical Analysis

Considering an effect size of 0.54 for the chemotherapy group on the cognitive global score based on previous meta-analyses,[30-34] a power of 80%, and an α of 0.05, the sample size calculation determined that 55 participants per group was necessary. To evaluate for differences between the groups, we used the Fisher exact test for categorical variables and an unpaired t test for continuous variables. Because the scoring of the neuropsychological tests differed, standardized scores (z-scores) were used to construct a composite score with equal weights for each test. The z-scores were

Table 2 Baseline Characteristics Stratified by Chemotherapy Status (n = 69)

Variable	All Patients	Chemotherapy		*P* Value
		No (CTh^-; n = 22)	Yes (CTh^+; n = 47)	
Age,[a] y	62.5 ± 9.4	65.8 ± 10.0	61.1 ± 8.8	.06
Female sex[b]	39.7	47.6	36.2	.43
Cancer stage[b]				<.0001
II (n = 44)	63.8	95.5	49.0	
III (n = 25)	36.2	4.5	51.0	
White race[b]	58.8	61.9	57.4	.79
Married	63.4	57.1	66.0	.59
Income				.74
< 2 Minimum wage	29.4	28.6	29.8	
2-5 Minimum wage	51.5	47.6	53.2	
> 5 Minimum wage	19.1	23.8	17.0	
Education,[a] y	7.6 ± 3.7	6.8 ± 2.8	7.9 ± 3.9	.22
Comorbidities, n	1.19 ± 1.14	1.10 ± 1.14	1.23 ± 1.16	.65
CCI ≥ 2	14.7	9.5	17.0	.71
Medications,[a] n	2.03 ± 2.09	1.90 ± 2.21	2.09 ± 2.06	.74
Smoking[b]				1.00
Never	54.4	57.1	53.2	
Current	5.9	4.8	6.4	
Former	39.7	38.1	40.4	
Alcohol use[b]	7.3	9.5	6.4	.64
Physical activity[b]	32.3	33.3	31.9	1.00
Hemoglobin,[a] g/dL	12.5 ± 1.7	12.3 ± 2.2	12.5 ± 1.4	.68
Body mass index,[a] kg/m^2	25.3 ± 3.5	25.9 ± 3.5	25.0 ± 3.6	.33
Interval between t1 and t2,[a] d	375 ± 29	377 ± 18	374 ± 33	.73
Apolipoprotein Eε4,[c] %	26	31.2	23.4	0.61

Data presented as mean ± standard deviation or %.
Abbreviations: CCI = Charlson comorbidity index; CTh, chemotherapy; t1 = baseline assessment; t2 = assessment 12 months after chemotherapy initiation.
[a]Unpaired *t* test.
[b]Fisher exact test.
[c]Total patients with apolipoprotein E genotyping was 69 and with the Eε4 alelle was 18.

obtained by calculating the difference of each participant score by the sample mean, divided by the sample standard deviation. For interpretative purposes, the composite score was rescaled to have a mean of 50 and a standard deviation of 10, such that a difference of 1 unit corresponded to 0.1 standard deviation.[58]

We used linear mixed models to investigate the association between cognitive performance and chemotherapy, adjusted for age, sex, education, and depressive symptoms at baseline. Voxel-based bicaudal *t* tests were used to analyze differences between the CTh^+ and CTh^- groups at baseline. All inferential analyses were performed in the per-protocol population (ie, those who had completed both t1 and t2 assessments). Analyses were performed using Stata, version 12.0 (StataCorp, College Station, TX). The α level was set at 0.05, and all tests were 2-tailed.

Results

From December 2012 to 2014, a total of 137 patients were approached, of whom 85 were enrolled and completed the initial neuropsychological assessment (59 in the CTh^+ group and 26 in the CTh^- [control] group). Because of study withdrawals, disease progression, and death, 69 participants (81%) finished the second evaluation (Figure 1).

The demographic data and baseline characteristics of the participants who completed both assessments, stratified by chemotherapy status, are listed in Table 2. The 2 groups were similar, except that the CTh^- patients were slightly older ($P = .06$). Most patients were male (60.3%) and elderly (mean age, 62.5 ± 9.4 years) and had a mean of 7.6 ± 3.7 years of education. The interval from t1 to t2 for the evaluations was ~1 year (mean, 375 ± 29 days), with no difference between the CTh^+ and CTh^- groups. Sixteen patients were lost during the follow-up period. Nevertheless, the participants who had not completed the study were similar to those who had completed the study regarding demographic data, clinical findings, and cognitive performance at baseline.

Considering the performance on each neuropsychological test at baseline, both groups had similar scores, except for the digit span-backward test (β, −1.03; 95% confidence interval [CI], −1.82 to −0.25; $P = .01$; Table 3). A significant difference was found in the cognitive performance between the 2 groups across time on executive function (β, −1.80; 95% CI, −3.50 to −0.11; $P = .04$). However, no

Table 3 Association Between Each Cognitive Tests and Chemotherapy Use During Follow-up (n = 69)

	Simple		Multiple[a]	
Variable	**β (95% CI)**	***P* Value**	**β (95% CI)**	***P* Value**
HVLT total				
Chemotherapy	1.20 (−2.53 to 4.93)	.52	0.79 (−2.80 to 4.37)	.66
Time	2.05 (0.25 to 3.84)	.03	2.32 (0.57 to 4.07)	.01
Chemotherapy*time	−0.49 (−2.65 to 1.67)	.65	−0.59 (−2.70 to 1.51)	.58
HVLT free				
Chemotherapy	−0.44 (3.54 to 7.51)	.71	−0.67 (−2.99 to 1.65)	.56
Time	0.62 (−0.49 to 1.72)	.27	0.73 (−0.35 to 1.82)	.18
Chemotherapy*time	0.57 (−0.76 to 1.90)	.39	0.56 (−0.75 to 1.87)	.40
HVLT recognition				
Chemotherapy	0.59 (−1.14 to 2.33)	.50	0.40 (−1.34 to 2.15)	.65
Time	0.38 (−0.46 to 1.22)	.37	0.43 (−0.43 to 1.29)	.32
Chemotherapy*time	−0.08 (−1.10 to 0.93)	.87	−0.10 (−1.13 to 0.93)	.85
BVMT total				
Chemotherapy	0.63 (−5.83 to 7.08)	.85	−1.84 (−7.88 to 4.20)	.54
Time	1.48 (−1.07 to 4.02)	.25	1.04 (−1.41 to 3.50)	.40
Chemotherapy*time	1.63 (−1.43 to 4.69)	.29	2.08 (−0.86 to 5.03)	.16
BVMT free				
Chemotherapy	0.55 (−1.92 to 3.02)	.66	−0.23 (−2.62 to 2.17)	.85
Time	0.71 (−0.33 to 1.76)	.18	0.64 (−0.41 to 1.69)	.23
Chemotherapy*time	0.29 (−0.97 to 1.54)	.65	0.36 (−0.90 to 1.62)	.57
BVMT recognition				
Chemotherapy	0.70 (−0.26 to 1.65)	.15	0.56 (−0.40 to 1.52)	.25
Time	0.14 (−0.34 to 0.62)	.55	0.13 (−0.35 to 0.61)	.59
Chemotherapy*time	−0.28 (−0.86 to 0.30)	.34	−0.27 (−0.85 to 0.32)	.36
Digit span-forward				
Chemotherapy	−1.15 (−3.30 to 0.99)	.29	−1.16 (−3.29 to 0.97)	.28
Time	0.29 (−0.73 to 1.30)	.58	0.39 (−0.63 to 1.40)	.45
Chemotherapy*time	0.40 (−0.83 to 1.62)	.52	0.29 (−0.93 to 1.51)	.63
Trail making A				
Chemotherapy	−14.60 (−42.53 to 13.32)	.30	−4.05 (−30.92 to 22.82)	.76
Time	3.29 (−7.47 to 14.04)	.54	4.04 (−6.84 to 14.92)	.46
Chemotherapy*time	−0.92 (−13.86 to 12.01)	.89	−1.59 (−14.65 to 11.47)	.81
Digit-symbol				
Chemotherapy	5.34 (−5.11 to 15.81)	.31	0.51 (−7.98 to 9.01)	.90
Time	1.45 (−1.45 to 4.35)	.32	1.29 (−1.66 to 4.25)	.38
Chemotherapy*time	−0.79 (−4.25 to 2.67)	.65	−0.46 (−3.98 to 3.05)	.79
Digit span-backward				
Chemotherapy	2.30 (0.76 to 3.85)	.004	2.03 (0.57 to 3.50)	.007
Time	0.57 (−0.11 to 1.25)	.10	0.53 (−0.12 to 1.19)	.11
Chemotherapy*time	−1.12 (−1.94 to −0.31)	.008	−1.03 (−1.82 to −0.25)	.01
Semantic verbal fluency				
Chemotherapy	1.50 (−2.01 to 5.02)	.40	1.20 (−2.37 to 4.76)	.50
Time	0.52 (−1.13 to 2.18)	.53	0.54 (−1.14 to 2.22)	.52
Chemotherapy*time	−0.80 (−2.80 to 1.20)	.43	−0.82 (−2.84 to 1.19)	.42
Phonemic verbal fluency				
Chemotherapy	0.69 (−5.70 to 7.08)	.83	−1.09 (−7.29 to 5.12)	.73
Time	0.52 (−2.03 to 3.08)	.68	0.62 (−1.94 to 3.18)	.63
Chemotherapy*time	0.52 (−.256 to 3.60)	.73	0.53 (−2.54 to 3.60)	.73

Table 3 Continued

Variable	Simple		Multiple[a]	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Trail making B				
Chemotherapy	−38.72 (−97.18 to 19.74)	.19	−12.73 (−64.90 to 39.45)	.63
Time	−16.29 (−39.56 to 6.98)	.17	−15.50 (−39.07 to 8.06)	.19
Chemotherapy*time	16.88 (−11.11 to 44.87)	.23	16.07 (−12.23 to 44.37)	.26
Stroop C				
Chemotherapy	−5.76 (−22.04 to 10.53)	.48	−0.79 (−16.49 to 14.92)	.92
Time	3.43 (−3.44 to 10.30)	.32	3.12 (−3.87 to 10.11)	.38
Chemotherapy*time	−4.89 (−13.12 to 3.35)	.24	−4.77 (−13.13 to 3.59)	.26

Abbreviations: BVMT = brief visuospatial memory test; CI = confidence interval; HVLT = Hopkins verbal learning test.
[a]Linear mixed models adjusted for age, sex, education, and depressive symptoms at baseline.

difference was found in the global composite score (β, −0.61; 95% CI, −1.88 to 0.66; $P = .34$), attention (β, 0.22; 95% CI, −1.89 to 2.33; $P = .84$), and memory (β, 0.03; 95% CI, −2.08 to 2.15; $P = .97$), after adjustment for age, sex, education, and depressive symptoms at baseline (Table 4). The performance on executive function was greater for the CTh^+ patients at t1 but had declined significantly more at t2 compared with the CTh^- group (Figure 2).

A subgroup of 44 participants had undergone brain MRI at t1 (29 patients from the CTh^+ group and 15 from the CTh^- group) and 32 had completed the second MRI acquisition at t2 (19 in the CTh^+ and 13 in the CTh^- group) and were included in the DTI analysis (Figure 1).

No statistically significant differences were found between the CTh^+ and CTh^- groups at baseline. Also, no statistically significant differences were found for all DTI indexes (FA, mean diffusivity, axial diffusivity, and radial diffusivity) in any WM regions between the CTh^+ and CTh^- groups between t1 and t2. Because no differences were found between the 2 groups between t1 and t2, we did not perform correlation analyses of the neuropsychological test results with the FA values from the DTI images.

APOE genotyping was available for all 69 patients, of whom 18 had ≥ 1 E4 allele (7 CTh^- and 11 CTh^+ patients; Table 2). The presence of the E4 allele did not influence the cognitive performance of the patients at baseline or at the follow-up assessments.

Discussion

To the best of our knowledge, this is the first longitudinal prospective study that showed a decline in executive performance after adjuvant 5-fluorouracil and oxaliplatin-based chemotherapy for CRC. Executive function is the ability to plan and organize tasks, problem solve, initiate appropriate action, and inhibit competing responses.[59] Our findings are consistent with those reported previously from 2 meta-analyses, which mostly analyzed studies of breast cancer survivors and not CRC patients.[30,32] In the present study, MRI did not show evidence of altered structural brain connectivity at baseline or during follow-up, and APOE polymorphisms were not predictive of overall cognitive dysfunction.

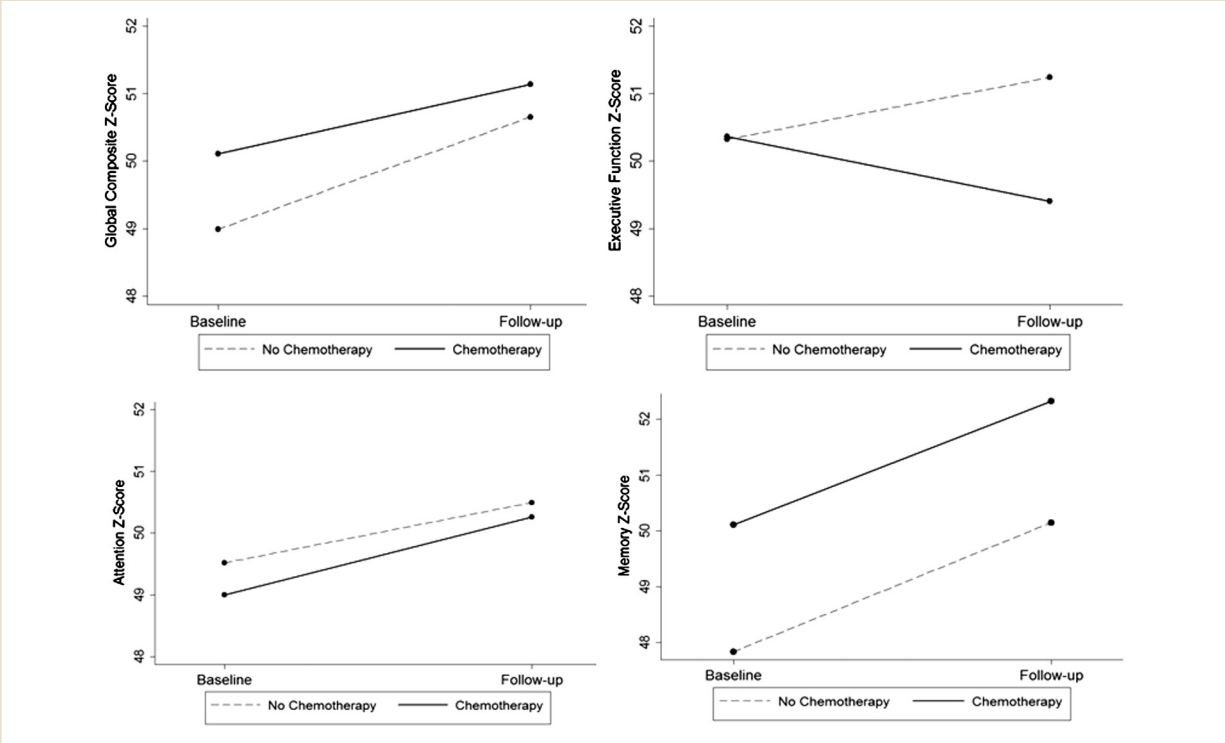
Two single-arm studies assessed the effects of chemotherapy in patients with CRC. The first study showed no decline in neurocognitive performance after adjuvant FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin).[37] However, the study was limited by the small sample size (n = 57), the lack of a control group, and the brief cognitive assessment used.[37] Cruzado et al.[60] reported impairment in verbal memory before and 6 months after chemotherapy, with a decline from baseline in 52% of the participants (n = 54). However, the lack of a control group left to question whether this effect had resulted from time or other confounding factors.[60] Recently, Vardy et al[36] assessed 289 patients with localized CRC (of whom 173 had received chemotherapy), 73 patients with limited metastatic or recurrent CRC, and 72 healthy controls. Patients with CRC had greater cognitive impairment at diagnosis and at every assessment ≤ 2 years of follow-up compared with normative data and healthy controls.[36] However, no significant effect was found from chemotherapy on cognition.[36] Also, the participants who completed more assessments showed less cognitive impairment than those who had withdrawn earlier ($P = .012$), which might have confounded the results. Despite the large number of patients in the study by Vardy et al,[36] the investigators did not explore the role of

Table 4 Association Between Cognitive Function and Chemotherapy Use During Follow-up (n = 69)

Variable	Simple		Multiple[a]		Effect Size (Cohen's D)
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	
Global composite score	−0.64 (−1.93 to 0.66)	.33	−0.61 (−1.88 to 0.66)	.34	0.18
Memory	−0.06 (−2.17 to 2.06)	.96	0.03 (−2.08 to 2.15)	.97	0.30
Attention	0.29 (−1.83 to 2.41)	.79	0.22 (−1.89 to 2.33)	.84	0.25
Executive function	−1.88 (−3.58 to −0.18)	.03	−1.80 (−3.50 to −0.11)	.04	0.36

Abbreviation: CI = confidence interval.
[a]Linear mixed models adjusted for age, sex, education, and depressive symptoms at baseline.

Figure 2 Cognitive Performance Stratified by Time for Global Score and Cognitive Domains: Attention, Executive Function, and Memory



chemotherapy on the cognitive performance of patients across the different cognitive domains.

The mechanisms underlying CRCI are largely unknown, and multiple mechanisms are probably involved.[61] Studies have shown that some chemotherapy agents such as 5-fluorouracil and capecitabine can penetrate the blood–brain barrier and cause direct neurotoxic damage.[62] Some reports have described cases of reversible posterior leukoencephalopathy syndrome associated with oxaliplatin, implying that this drug also penetrates the blood–brain barrier and could contribute to central nervous system toxicity in some patients.[63,64] Other candidate mechanisms include immune dysregulation and increased release of inflammatory cytokines, DNA damage due to oxidative stress, and vascular damage.[59] Many risk factors such as age,[25,65] type and dose of chemotherapy regimen, and genetic factors could play significant roles in the development of chemobrain.[58]

DTI allows for detection of brain injury earlier than conventional MRI sequences and also appears more sensitive for detecting damage of WM compared with any other imaging method.[66] The FA is a scalar measure that reflects the microstructural geometry and is notably high in the normal WM but is usually lower in damaged WM. Deprez et al[28] conducted the first longitudinal DTI investigation of WM changes induced by systemic chemotherapy in 34 breast cancer patients before and 3 to 5 months after the start of treatment with 5-flurouracil, epirubicin, and cyclophosphamide with or without paclitaxel compared with 16 nonexposed breast cancer patients and 19 healthy controls at matched intervals. No baseline differences were found among the 3 groups. However, after treatment, only the chemotherapy group demonstrated decreased FA values in the frontal, parietal, and occipital WM regions.[28] However, the same group reassessed most of these patients 3 to 4 years after treatment, and they recently reported recovery of FA changes in the brain parenchyma and improvements in cognitive performance.[67]

We performed the current leading method of voxelwise analysis (ie, tract-based spatial statistics) to study WM changes in CRC patients with and without chemotherapy exposure. We found no statistically significant differences in DTI parameters in both groups between t1 and t2. Only a smaller subset of the individuals included in the present study (19 CTh^+ patients and 13 CTh^- controls) completed the MRI evaluation at both evaluation points, which could have limited the power of the statistical analyses. Moreover, it is not clear whether transient FA changes had occurred within the study period.

The strengths of the present study included its longitudinal prospective design, the presence of a control group with cancer and characteristics similar to those of the patient group, and the use of a comprehensive battery of neuropsychological tests sufficiently sensitive to detect the subtle changes in cognitive function. In addition, the enrollment of consecutive patients avoided a selection bias, and all patients received similar chemotherapy regimen in accordance with institution guidelines. Because our sample included both male and female patients, who had not received hormonal therapy, our

results were not biased by this potential confounding factor as were previous studies of patients with breast cancer.

However, the present study had some limitations. First, our final sample size was smaller than planned, which reduced the power of the study. This problem highlights the challenges associated with conducting research in cancer survivors. The post hoc estimated power of our sample with an effect size of d = 0.5 was only 56%, which might have influenced our negative results on the global composite score. However, we were able to find statistically significant results for the executive function domain ~12 months after the first assessment. Whether these effects are transient or permanent remains uncertain. Some studies showed improvement after 1 year[68]; however, others reported permanent deficits in the long term (10-20 years).[24,69] Studies with multiple points and long-term assessment of cognitive function after chemotherapy are crucial to clarifying the relationship between chemotherapy exposure and cognitive impairment.

The control group in our study included cancer patients who had not received chemotherapy. Although their performance was similar to that of the CTh^+ patients at baseline, we did not compare their data with data from healthy matched controls. Recent research has shown that cancer patients might present with compromised cognitive function before chemotherapy, raising the possibility that this adverse effect has been caused in some extent to the disease process itself.[9,17,26,36]

Another consideration is the duration of chemotherapy and its effect on cognitive function. Most CRCI studies of cancer survivors considered the effects of 6 months of adjuvant chemotherapy, which is the standard duration for most solid tumors. Specifically for CRC, this has been challenged by the IDEA (international duration evaluation of adjuvant chemotherapy) pooled analysis, which demonstrated that 3 months of oxaliplatin and capecitabine offers very similar benefits in disease-free survival at 3 years compared with 6 months of FOLFOX but significantly less neurotoxicity.[70] Future studies should evaluate whether our finding of executive dysfunction would also be observed in CRC patients treated with a shorter duration of chemotherapy.

Conclusion

Our study has shown that adjuvant chemotherapy for CRC with 5-fluorouracil with or without oxaliplatin can cause a decline in executive function 12 months after treatment initiation. This finding could affect the quality of life of survivors and should be studied further. If our findings are confirmed by future studies, the risk of CRCI should be discussed with patients when recommending adjuvant chemotherapy for CRC.

Clinical Practice Points

- Cognitive dysfunction can develop after chemotherapy in cancer survivors, potentially impairing their quality of life and/or socioeconomic activities.
- Our study has demonstrated that the receipt of fluoropyrimidine-based adjuvant chemotherapy is associated with a decline in the executive function of patients with stage II or III CRC after 12 months of treatment compared with patients who do not receive chemotherapy.
- Although this new finding should be investigated further in larger cohorts with longer follow-up periods, these data could be used to support 3 versus 6 months of adjuvant chemotherapy for stage III CRC.

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Disclosure

The authors declare that they have no competing interests.

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