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Original Article

Neurocognitive Effects of Chemotherapy for Colorectal Cancer: A Systematic Review and a Meta-Analysis of 11 Studies

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Purpose Chemotherapy-related cognitive impairment (CRCI) is a controversial concept not much explored on colorectal cancer patients.

Materials and Methods We identified 11 prospective studies: eight studies on 696 colorectal cancer patients who received chemotherapy and three studies on 346 rectal cancer patients who received neoadjuvant chemoradiotherapy. Standardized mean differences (SMDs) of neuropsychological test results and the cognitive quality-of-life scale were calculated using random effect models. A meta-regression was conducted to investigate the association between mean study population age and effect sizes.

Results The association between chemotherapy and cognitive impairment was not clear in colorectal cancer patients (SMD, 0.003; 95% confidence interval, −0.080 to 0.086). However, a meta-regression showed that older patients are more vulnerable to CRCI than younger patients (β=−0.016, $p < 0.001$).

Conclusion Chemotherapy has an overall positive negligible effect size on the cognitive function of colorectal patients. Age is a significant moderator of CRCI.

Key words Cognitive dysfunction, Colorectal neoplasms, Drug therapy, Meta-analysis

Introduction

Colorectal cancer is the third most common and second most deadly cancer worldwide. In men, it is the third most commonly diagnosed cancer and the leading cause of cancer death while in women, it is the second most frequently diagnosed and the second deadliest cancer, second to only breast cancer [1].

Chemotherapy has been suggested to cause chemotherapy-related cognitive impairment or the so-called chemo-brain. A study at the Netherlands Cancer Institute reported cognitive impairment in 83 patients with breast cancer. Those who received high-dose chemotherapy were at a higher risk than those who received standard-dose chemotherapy, who in turn were at a higher risk than controls [2]. A meta-analysis of 29 studies investigating the effects of chemotherapy on cognitive impairment regardless of cancer type suggested that chemotherapy has negative effects on several domains of neurocognitive function, including executive function, verbal memory, and motor function [3].

However, whether "chemo-brain" occurs in colorectal cancer patients is controversial. Some studies have reported that chemotherapy has a negative impact on neurocognitive functions in these patients [4], but others have suggested that "chemo-brain" does not represent a major issue in colorectal cancer [5]. Common chemotherapy regimens for colorectal cancer patients, which often include oxaliplatin and 5-fluorouracil (5-FU) [6], may induce chemotherapy-related neurotoxicity involving the central nervous system [7,8]. Therefore, assessing the negative impacts of chemotherapy on neurocognitive function is crucial for developing preventive measures including behavioral pharmacological treatment [9], as well as rehabilitation programs after the treatment [10].

The noted disparity in the findings regarding "chemo-brain" in colorectal cancer patients may be attributed to the heterogeneity in the populations sampled in previous studies. Numerous studies on "chemo-brain" have suggested that older patients are more prone to cognitive impairment after chemotherapy than younger patients [11]. While this is probably due to older patients' lower cognitive reserves at treatment initiation [12], more research on colorectal cancer patients is required to reach any such conclusion.

We aimed to assess the negative impacts of chemotherapy on neurocognitive function in colorectal cancer patients by

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conducting a systematic review of published manuscripts on the topic. Additionally, we sought to identify population characteristics responsible for the observed heterogeneity in "chemo-brain" findings.

Materials and Methods

1. Search strategy and selection criteria

Three databases were searched on January 9, 2019 by SYH: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL)/Cochrane Database of Systemic Reviews. The search terms contained keywords related to cancer ("cancer" "tumor" "neoplasm" "malignancy"), colorectal ("colon" "rectal" "colorectal"), chemotherapy ("chemotherapy" "chemoradiotherapy" "antineoplastic protocols" "chemotherapy, adjuvant"), cognition, cognitive domains, and neuropsychological batteries measuring cognition ("cognition" "cognition disorders" "cognitive dysfunction" "cognitive impairment" "memory" "orientation").

A total of 1,224 articles were identified: 140 from PubMed, 957 from Embase, and 127 from the Cochrane Database of Systematic Reviews. After removing 58 duplicates, 1,166 articles were deemed eligible for title screening (by SYH, BH, DL, JY, SR), 264 for abstract screening (by SYH, BH, DL, SK), and 37 for full-text screening (done by SYH, KK). The main author (SYH) made decisions on initial article inclusion and continued inclusion at each phase. The process of excluding articles was performed by two independent researchers, with final decisions made by a third author (SYH) in cases of disagreement.

To be included in the final analysis, the studies had to include cancer patients receiving chemotherapy (exposure) and measurements of cognitive function or perceived cognitive impairment (outcome). The included studies presented measures of cognitive function for colorectal cancer patients at baseline (before chemotherapy) and after chemotherapy. Through title and abstract screening, we excluded 1,129 studies, leaving 37 studies for full-text review (Fig. 1). After full content review, an additional 28 articles were excluded: three were only abstracts (provided insufficient data), three were from the same cohort, nine had insufficient details regarding cognitive function measurements, five only contained the results of measurements prior to chemotherapy, seven were cross-sectional studies, and one did not report the standard deviations. The authors of all studies with insufficient data were contacted for additional data.

To identify papers containing data on colorectal cancer as well as other types of cancer, a separate search was performed, and 23 authors were separately contacted for data on colorectal cancer patients. As one author sent the original data, one additional study [13] was included; one study [14]

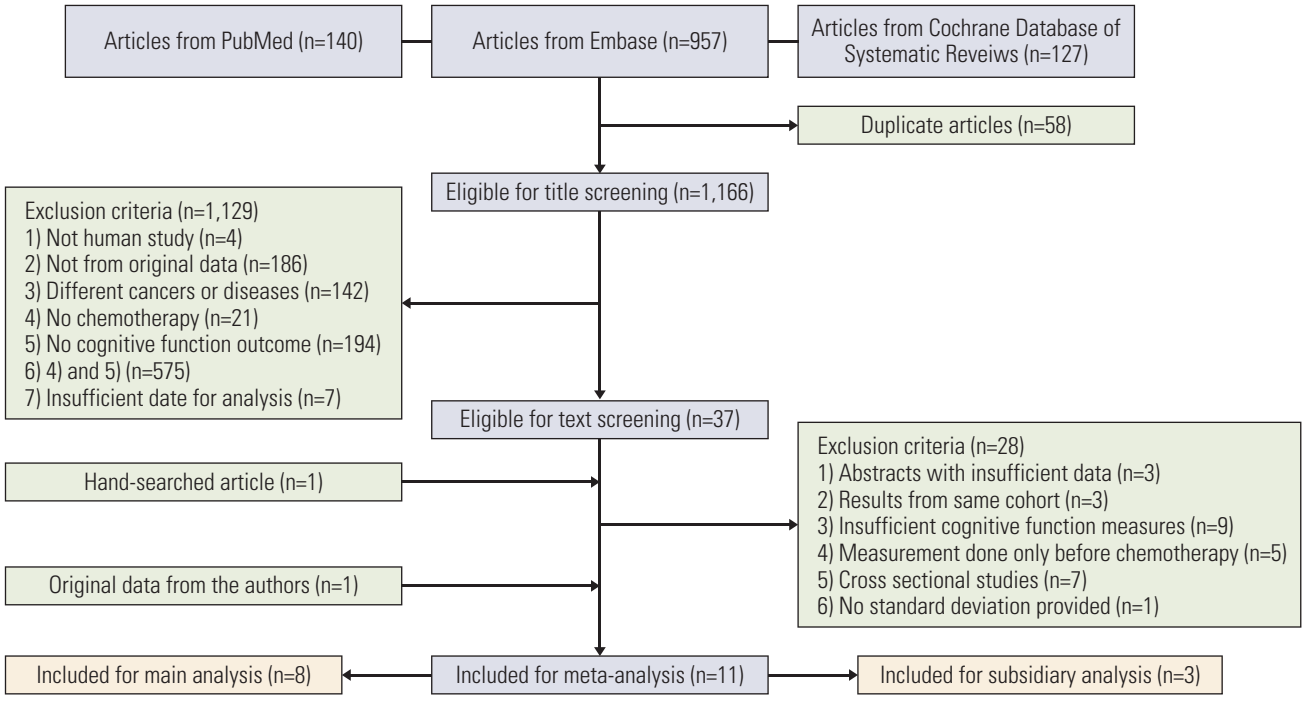

Fig. 1. Flow chart for inclusion of articles for meta-analysis.

was newly included by manual search, resulting in a total of 11 studies. [4,5,13-21] Among them, eight studies pertained to the treatment of colon cancer and rectal cancer patients with chemotherapy, and the other three pertained to the treatment of rectal cancer patients with neoadjuvant chemotherapy.

2. Data analysis

Thirty-five clinical neuropsychological tests were conducted across the five studies. To facilitate analysis, measures were rearranged into six domains: attention, executive function, processing speed, visuospatial processing, language, and memory. The memory domain comprised four subdomains: verbal, visuospatial, short-term, and long-term. Each test was rearranged according to its most frequently assigned domain based on a meta-analysis assessing how previous meta-analyses assigned neuropsychological tests to each domain (provided by Horowitz et al., 2019 [22]) (S1 Table). This was done in order to classify the neuropsychological measures into six domains.

Three studies included in the final analyses assessed cognitive function by The European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ C30) scale. The EORTC-QLQ C30 scale is a scale that measures the quality of life of cancer patients undergoing clinical trials [23]. The EORTC-QLQ C30 version 3·0 includes five functional subscales (physical, role, cognitive, emotional, and social) and nine symptom subscales. Results from cognitive subscale was selected.

Overall cognitive function effect sizes were estimated with the standardized mean difference (SMD) method. We subtracted the baseline score from the retest score and divided the difference by the pooled standard deviations to estimate the SMD. For studies that included more than one follow-up assessment, data from the first retest were used to minimize reductions in sample size. For five studies with objective neurocognitive function test results, since types of neurological tests were different for each study, the effect size of each test result was pooled to estimate the SMDs and 95% confidence intervals (95% CIs). For six studies, effect sizes were defined as SMDs for responses from the cognitive domain of quality of life (QoL) reports.

A meta-analysis using random and fixed effects models was conducted to pool the SMDs of each study and estimate the weighted average effect size. The Q and Higgins I^2 statistics were calculated to evaluate the heterogeneity in the included studies [24]. To estimate the effect of differences in cancer stage, we conducted sensitivity analysis excluding the results from advanced colorectal cancer (Vardy et al. [5], metastatic and Mayrbaurl et al. [17]). Publication bias was visually assessed by plotting effect size against sample size (i.e., funnel plot). A subgroup analysis was conducted by stratifying studies according to two methods of assessing cognitive function: objective neurocognitive tests vs. subjective QoL reports. An additional subgroup analysis was conducted for three studies in which rectal cancer patients received neoadjuvant concurrent chemoradiation therapy (CCRT). Additionally, as age is an important effect modifier of cognitive function, we conducted a meta-regression of the mean baseline population age versus effect size.

Quality assessment was conducted with the Newcastle-Ottawa Scale (NOS) for prospective studies. The NOS is a convenient tool comprising four items for selection, one item for comparability, and three items for outcome [25]. The number of stars on each question represents the NOS grade. A maximum of one star can be given to each item, except the comparability item, allowing for a maximum of two stars. Thus, the maximum NOS grade is nine [25]. The strengths of the NOS are clear in the context of meta-analyses in psychiatry. In this domain, diagnoses, responses, and outcomes are dependent on clinical evaluations [26]. Two independent researchers performed each assessment (SYH, BH). We conducted another sensitivity analysis excluding the results from articles with NOS scores of 5 or lower. All processes of data searching and analyzing were conducted in accordance of PRISMA protocol.

Results

A pooled effect size was calculated based on 12 effect sizes from 11 studies. All studies included in the analyses were longitudinal prospective studies. Vardy et al. (2015) [5] reported on two subgroups: localized colorectal cancer patients and metastatic colorectal cancer patients, and the findings of these two studies were analyzed as separate study estimates. Five studies, Cruzado et al. (2014) [4], Vardy et al. (2015) [5], Sales et al. (2019) [16], Andreis et al. (2013) [15], and Anstey et al. (2015) [13] measured cognitive function with clinical neuropsychological tests. Mayrbaurl et al. (2016) [17], Lee et al. (2016) [14], and Tsunoda et al. (2010) [18] used the EORTC-QLQ C30 Cognitive Functioning Scale to measure subjective cognitive function. Cruzado et al. (2014) [4] and Vardy et al. (2015) [5] also reported results from the EORTC-QLQ-C30 Cognitive Functioning Scale but only included neuropsychological test results (Table 1).

1. Study characteristics

In total, 696 patients—402 men (57.76%) and 294 women (41.67%)—participated in eight studies. The mean age was 59.96 years; mean education duration was 11.31 years. The shortest follow-up period was approximately 6 months

Table 1. Study characteristics of the studies included in this meta-analysis

Study	Study designe	No. of initial participants	Follow-up period (mo)	Age (yr), mean±SD or median (range)	Male, n (%)	Education (yr)	Cancer site	Cancer stage	Chemotherapy regimen	Neuropsychological measurement	Covariates	NOS score
Main analysis												
Andreis et al. (2013) [15]	Prospective study	47[a)]	6	58.68±9.62	16 (34.04)	9.43 (3.91)	Colon (47)	3 (47)	FOLFOX4 ǀ oxaliplatin 980 (364), 5-FU 19,103 (6,840), 5-FU bolus 6,745 (2,431), 5-FU continuous infusion 14,075 (4,642), n. administration 11.42 (1.5)	Clock Drawing Test, Rey Auditory Verbal Learning Test (call/recall), Rey Complex Figure, (copy/recall) TMT A, TMT B,	Age, education, sex	7
Vardy et al. (2019) (localized) [5]	Prospective study	173	6	57.0 (23-75)	117 (67.63)	13.8 (3.3)	Colon (104), rectum (66)	1 (2), 2 (46), 3 (125)	Adjuvant (123), neoadjuvant (46), unknown (4) ǀ FU (54), oxaliplatin (72), chemoradiation (44), missing (3)	Clinical NP Tests (Letter-Number test, Digit span test, Spatial Span test, HVLT total, HVLT delayed, BVMT total, BVMT delayed, Digit Symbol test, TMT A, TMT B), Cambridge Neuropsychological Test Automated Battery (CANTAB)	Age, sex, education, time between assessments, practice effect	9
Vardy et al. (2015) (metastatic) [5]	Prospective study	73	6	55.5 (28-75)	40 (54.79)	13.7 (3.4)	Colon (54), rectum (16)	3 (4), 4 (69)	None (1), FU (4), oxaliplatin (36), chemoradiation (2), irinotecan (20), other (2), missing (4)			

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Table 1. Continued

Study	Study designe	No. of initial participants	Follow-up period (mo)	Age (yr), mean±SD or median (range)	Male, n (%)	Education (yr)	Cancer site	Cancer stage	Chemotherapy regimen	Neuropsychological measurement	Covariates	NOS score
Cruzado et al. (2014) [4]	Prospective study	81	6	66.96±9.52	50 (61.73)	6.9 (4.1)	-	1 (28), 2 (53)	Oxaliplatin plus 5-FU/leucovorin (FOLFOX4) adjuvant CT regimen within 6 to 8 weeks post-surgery ǀ no. of chemotherapy 11.80 (0.54), dosage of oxaliplatin mg/m^2 1,003.20 (129), total dose of 5-FU mg/m^2 21,690 (3,744)	TMT A, TMT B, Interference score of the Stroop Color and Word Test, Digit Symbol test, Verbal memory subtest of the Barcelona test (Immediate/Delayed memory), Luria Memory Words Test	Age, education, sex	6
Sales et al. (2019) [16]	Prospective study	47	12	61.1±8.8	30 (63.83)	7.9 (3.9)	-	2 (23), 3 (24)	6 cycles (6 mo) of 5-FU, leucovorin with or without oxaliplatin	HVLT, BVMT, Digit span-forward, TMT A, TMT B, Digit symbol test, Digit span (backwards), Semantic verbal fluency (animals), Stroop C test, Phonemic verbal fluency	Age, sex, education, depressive symptoms at baseline	8
Anstey et al. (2015) [13]	Prospective study	20	48	-	-	-	-	-	-	TMT A, TMT B, California Verbal Learning Test (Immediate/Delayed), Symbol-Digit-Modality test, Simple/choice reaction time, Verbal Fluency (F words, A words)	Unadjusted[b)]	6

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Table 1. Continued

Study	Study designe	No. of initial participants	Follow -up period (mo)	Age (yr), mean±SD or median (range)	Male, n (%)	Education (yr)	Cancer site	Cancer stage	Chemotherapy regimen	Neuropsychological measurement	Covariates	NOS score
Mayrbaurl et al. (2016) [17]	Prospective study	100	3 cycles[c]	66.4±10.6	60 (60)	-	-	Advanced colorectal cancer	First-line palliative 73 (FU FA oxaliplatin 16.7%, FU leucovorin 5.3%, FU FA irinotecan panitumumab 15.3%, FU FA oxaliplatin bevacizumab 12.5%) Second-line palliative 63 (FU FA irinotecan 18.3%, panitumumab 15%, FU FA irinotecan cetuximab 11.7%, FU FA oxaliplatin bevacizumab 10%) Third-line or more palliative 47 (panitumumab 17.6%, FU FA bevacizumab 17.6%, FU FA oxaliplatin 12.2%, FU FA oxaliplatin bevacizumab 9.5%)	EORTC-QLQ C30 Cognitive functioning	-	4
Lee et al. (2016) [14]	Prospective study	56	6 cycles[c]	59.5±11.5	31 (55.36)	None 8 elementary school 17 middle school 10 high school 11 college or more 10 (people)	Rectal (56)	2 (16), 3 (40), 4 (9)	6 cycles of FOLFOX	EORTC-QLQ C30 Cognitive functioning	-	4

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Table 1. Continued

Study	Study designe	No. of initial participants	Follow-up period (mo)	Age (yr), mean±SD or median (range)	Male, n (%)	Education (yr)	Cancer site	Cancer stage	Chemotherapy regimen	Neuropsychological measurement	Covariates	NOS score
Tsunoda et al. (2010) [18]	Prospective study	99	7	65±10	58 (58.59)	-	Colon (59), rectal (40)	2 (49), 3 (50)	Oral uracil/tegafure dose 300 mg/m^2/day, oral leucovorin dose of 75 mg/day on days 1-28, followed by a 7-day rest (35 days/cycle ×5 cycles)	EORTC-QLQ C30 Cognitive functioning	-	5
Subsidiary analysis												
Couwenberg et al. (2018) (LAR) [19]	Prospective study	134	3	64 (38-83)	93 (69.4)	-	Rectal (134)	cT2 (16), cT3 (104), cT4 (14), cN0 (16), cN1 (55), cN2 (63), cM0 (121), cM1 (12) M stage unknown (1)	-	EORTC-QLQ C30 Cognitive functioning	-	6
Couwenberg et al. (2018) (APR) [19]	Prospective study	119	3	66 (26-87)	91 (76.5)	-	Rectal (119)	cT1 (1), cT2 (15), cT3 (83), cT4 (20), cN0 (21), cN1 (51), cN2 (47), cM0 (113), cM1 (4), M stage unknown (2)	-	EORTC-QLQ C30 Cognitive functioning	-	

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Table 1. Continued

Study	Study designe	No. of initial participants	Follow -up period (mo)	Age (yr), mean±SD or median (range)	Male, n (%)	Education (yr)	Cancer site	Cancer stage	Chemotherapy regimen	Neuropsychological measurement	Covariates	NOS score
Souza et al. (2018) [20]	Prospective study	29	3	50.8±11.4	11 (38)	-	Rectal (29)	T3, T4, N+	5-FU 350 mg/m^2 (1st, 5th day)	EORTC-QLQ C30 Cognitive functioning	-	5
Bencova et al. [21] (men)	Prospective study	43	-	range (54-76)	43	-	Rectal (43)	T3, T4	5-FU 350 mg/m^2/day	EORTC-QLQ C30.3 Cognitive functioning	-	3
Bencova et al. [21] (women)	Prospective study	21	-	-	-	-	Rectal (21)	T3, T4	5-FU 350 mg/m^2/day	EORTC-QLQ C30.3 Cognitive functioning	-	

5-FU, 5-fluorouracil; APR, abdominoperineal resection; BVMT, Brief Visuospatial Memory Test; CT, computed tomography; EORTC-QLQ C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FA, folinic acid; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin regimen; HVLT, Hopkins Verbal Learning Test; LAR, low anterior resection; NOS, Newcastle-Ottawa Scale; SD, standard deviation; TMT, Trail Making Test. [a]57 patients were initially enrolled and assessed at the baseline, but 10 participants dropped out due to acute complications. Demographic characteristics of only 47 participants were gathered, [b]Authors of the study have provided original data on our request, [c]One cycle ≈ one month in average.

(range, 3 to 48 months) for five studies. The more common cancer among patients was colon cancer (59.7%). The most prevalent stage was stage 3 (49.6%), followed by stage 2 (32.0%), and stage 4 (13.3 %). The most frequent chemotherapy agents used were oxaliplatin, 5-FU, and irinotecan; the most common chemotherapy regimen was FOLFOX/FOLFOX4. Studies included in the main analyses were conducted on locally advanced stage colorectal cancer patients, except for Vardy et al. [5] (stage 3 and 4) and Mayrbaurl et al. [17] (advanced colorectal cancer). Both studies did not show significant results in accordance of cancer stages. The follow-up period between cognitive function assessments were mostly 6 months [4,5,15] except for Sales et al. [16] (12 months), Anstey et al. [13] (48 months), Mayrbaurl et al. [17] (3 cycles, which is about 3 months) and Tsunoda et al. [18] (7 months). There was no apparent association between follow-up period and effect size (β=–0.007, p=0.297). NOS scores of studies which utilized EORTC-QLQ C30 scales ranged from 4 to 5, which were significantly lower compared to the score range of 6 to 9 in studies with objective tools for cognitive function assessment (Table 1).

2. Effect sizes of overall cognitive function

Table 2 and Fig. 2 shows the standardized mean effect sizes calculated using fixed and random effects models. Results from random effects model did not support cognitive impairment after chemotherapy (SMD, 0.003; 95% CI, –0.219 to 0.249). Overall heterogeneity of the studies was moderately high (Higgins I^2=60%).

Results from the subgroup analyses showed no cognitive impairments both in studies with objective cognitive function assessment (SMD, 0.000; 95% CI, –0.093 to 0.093) and studies with subjective cognitive function (SMD, 0.015; 95% CI, –0.219 to 0.249) were both insignificant. Studies that measured subjective cognitive function with the EORTC-QLQ C30 showed higher variance in scores.

3. Publication bias

Fig. 3 shows the Funnel plot of eight studies that are included in the final analyses. Egger's test, used to assess publication bias, showed no indications of asymmetry (p=0.277) (Fig. 3). We concluded that there was no evidence for publication bias.

4. Results by cognitive function domains

Clinical neuropsychological tests were divided into six cognitive domains, with the memory domain further divided into four sub-domains. The SMDs (95% CI) of the four domains showed significant results, with a mild increase in cognitive function: processing speed (SMD, 0.101; 95% CI, 0.007 to 0.196); visuospatial processing (SMD, 0.141; 95% CI,

Table 2. Standardized mean differences for changes in neurocognitive function after chemotherapy in colorectal cancer patients (n=696)

	No. of initial participants	Follow-up (mo)	Male (%)	SMD	95% CI	p-value
Objective						
Andreis et al. [15]	47	6	34.0	0.023	–0.094 to 0.140	0.697
Vardy et al. [5], localized	173	6	67.6	0.057	0.011 to 0.102	0.016
Vardy et al. [5], metastatic	73	6	54.8	0.060	–0.006 to 0.126	0.075
Cruzado et al. [4]	81	6	61.7	–0.173	–0.289 to –0.057	0.003
Sales et al. [16]	47	12	63.8	0.099	–0.009 to 0.207	0.074
Anstey et al. [13]	20	48	N/A	–0.164	–0.387 to 0.060	0.151
Subtotal (I^2=73%)	441					
Fixed				0.037	0.004 to 0.069	0.026
Random				0.000	–0.093 to 0.093	0.998
Subjective						
Mayrbaurl et al. [17]	100	3 cycles[a)]	60.0	–0.214	–0.606 to 0.178	0.286
Lee et al. [14]	56	6 cycles[a)]	55.4	0.104	–0.267 to 0.475	0.583
Tsunoda et al. [18]	99	7	58.6	0.098	–0.169 to 0.217	0.324
Subtotal (I^2=0%)	255					
Fixed				0.024	–0.170 to 0.217	0.094
Random				0.015	–0.219 to 0.249	0.601
Total (I^2=60%)	696					
Fixed				0.036	0.005 to 0.068	0.025
Random				0.003	–0.219 to 0.249	0.939

CI, confidence interval; SMD, standardized mean difference. [a)]One cycle ≈ one month in average.

0.020 to 0.261); verbal memory (SMD, 0.156; 95% CI, 0.002 to 0.310); and visuospatial memory (SMD, 0.216; 95% CI, 0.070 to 0.363) (Table 3). Visuospatial memory showed a positive and small effect size, while the processing speed, visuospatial processing, and verbal memory domains showed a positive effect size that was negligible [27].

5. Age and cognitive impairment

The estimated regression coefficients for the effect of age on SMDs were statistically significant (β=–0.016, $p < 0.001$) (Fig. 4). Although the baseline characteristics of the cohort of Anstey et al. (2015) [13], has not been included, the cohort was comprised adults aged ≥ 60 years and showed a negative overall effect size.

6. Sensitivity analyses

Results from sensitivity analysis without results from advanced colorectal cancer was not significantly different compared to main analysis (random effects model: SMD, 0.005; 95% CI, –0.087 to 0.097) (S2 Fig.). Meta-regression from this scenario also provided consistent results with main meta-regression (β=–0.016, p=0.001) (S3 Fig.). In sensitivity analysis without results from studies with NOS of 5 or lower, merged effect of chemotherapy on cognitive function did not differ from main analysis as well (random effects model: SMD, 0.000; 95% CI, –0.093 to 0.093) (S4 Fig.). Meta-regression from this scenario was also similar to that of main analysis (β=–0.017, $p < 0.001$) (S5 Fig.).

7. Chemotherapy and CCRT

The results of the three studies on rectal cancer patients receiving neoadjuvant CCRT are presented in S6 Table. These studies employed the EORTC-QLQ C30 Cognitive Functioning Scale. Results from the three additional studies were also insignificant (–0.321 [–0.776 to 0.133]). The three studies showed high heterogeneity (Higgins I^2=79%).

Discussion

Overall, chemotherapy had a negligible positive effect on the neurocognitive functions of colorectal cancer patients. The domains of visuospatial memory, verbal memory, processing speed, and visuospatial processing showed improvements in function, with negligible to small effect sizes. Several potential moderators were analyzed to identify the factors responsible for the previously observed discrepancies in study results. Age was found to moderate the effects of chemotherapy on cognitive function.

The observed slight improvement in cognitive function

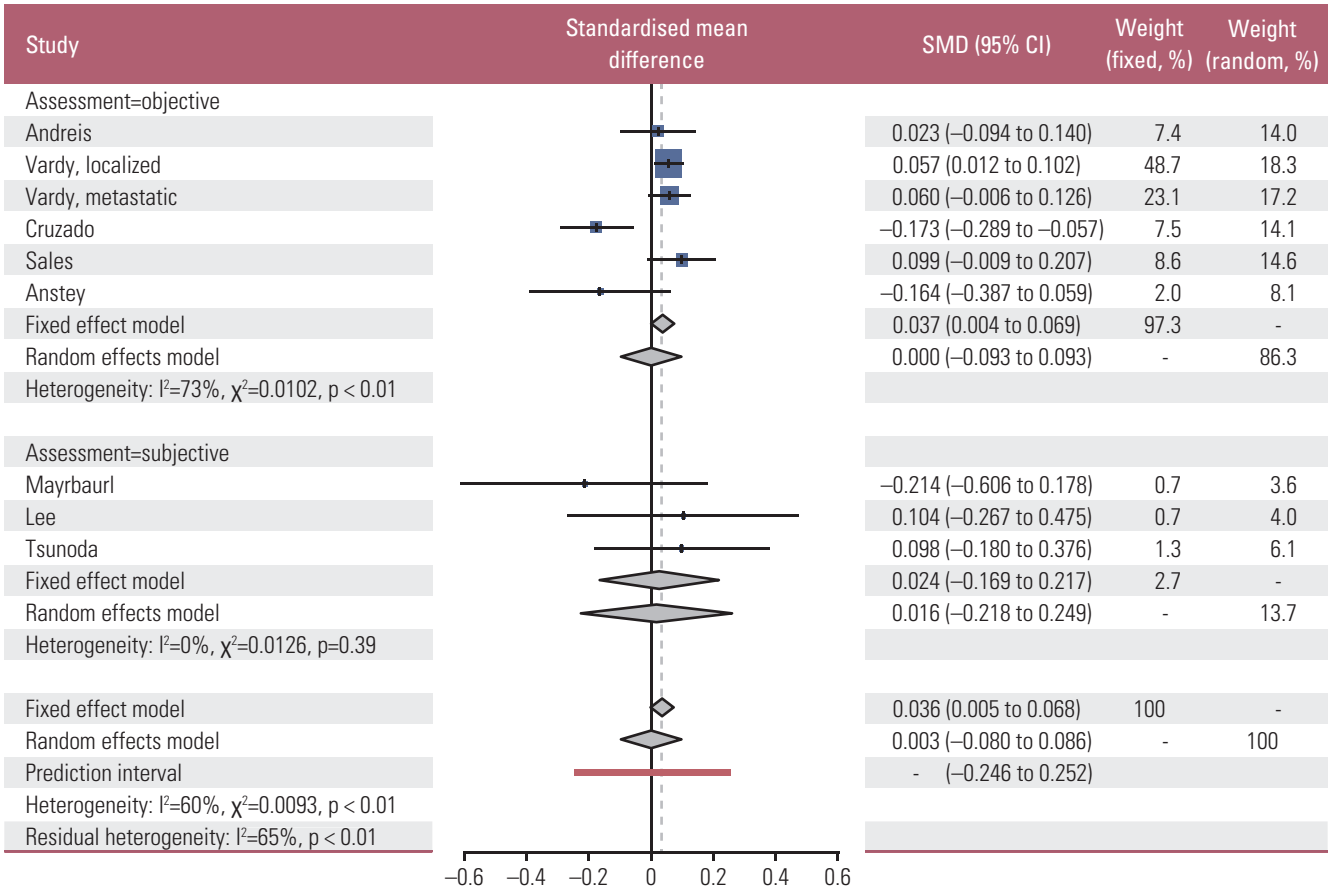

Fig. 2. Standardized mean differences for changes in neurocognitive function after chemotherapy in colorectal cancer patients (n=706). CI, confidence interval; SMD, standardized mean difference.

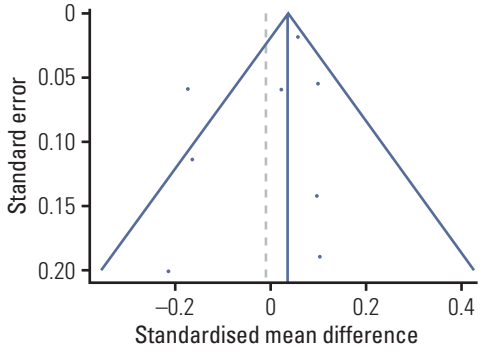

Fig. 3. Funnel plot of studies included in the final analyses.

among patients after chemotherapy is inconsistent with the results of previous meta-analyses [3,28-34]. This inconsistency may be due to the fact that previous meta-analyses focused on cross-sectional studies, while our study is limited to prospective studies. A meta-analysis of 44 longitudinal studies primarily investigating testicular and breast cancer showed improvement, supporting our results [35]. Effect sizes in this meta-analysis were small to moderate in size, especially in domains such as memory (verbal memory, visuospatial memory, and short-term memory), attention, and language [35]. The difference in study design leads to two subsequent disparities. First, in longitudinal studies, the "practice effect," an increase in a participant's cognitive test score due to repetition, is a variable that could complicate the interpretation of cognitive test results [36-39]. Repetition of verbal memory tests along with tests of psychomotor speed, executive function, and language [40], has been shown to produce practice effects [41]. And only one study [5] included in our analysis adjusted for this practice effect. Also, in cross-sectional designs, noted significant cognitive impairment in those receiving chemotherapy are relative to healthy controls or cancer patients who had not received any treatment. Our meta-analysis examined only longitudinal studies with repeated assessments, which could lead to direct changes in cognitive function after the treatment [42].

Table 3. Standardized mean differences for changes in neurocognitive function after chemotherapy in colorectal cancer patients, by cognitive function domain (n=441)

Cognitive function domain	No. of studies	No. of study population	SMD	95% CI	I^2
Attention	6	441	–0.017	–0.098 to 0.063	< 0.001
Executive function	6	441	0.060	–0.088 to 0.207	25.6
Processing speed	5	393	0.101	0.007 to 0.196	< 0.001
Visuospatial processing	3	303	0.141	0.020 to 0.261	< 0.001
Language	1	47	0.025	–0.261 to 0.311	< 0.001
Memory	6	441	0.036	–0.048 to 0.121	57
Verbal memory	3	374	0.156	0.002 to 0.310	18.2
Visuospatial memory	4	340	0.216	0.070 to 0.363	< 0.001
Short-term memory	6	441	0.005	–0.133 to 0.143	49.9
Long-term memory	5	393	–0.076	–0.244 to 0.091	71.6
Overall, fixed	6	441	0.037	0.004 to 0.069	73
Overall, random	6	441	0.000	–0.093 to 0.093	73

CI, confidence interval; SMD, standardized mean difference.

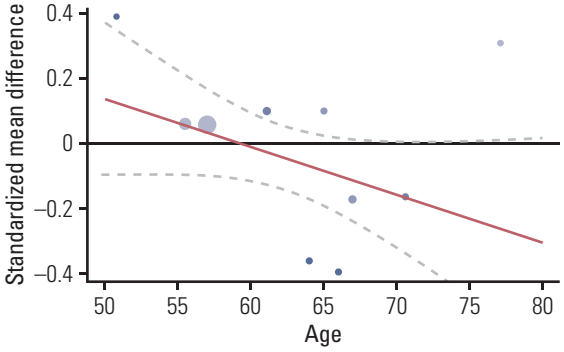

Fig. 4. Meta-regression plots for mean age of participant versus standardized mean difference.

In addition to chemotherapy, several factors associated with cancer itself can affect cognitive impairment in cancer patients, such as the psychosocial distress associated with a cancer diagnosis and the general weakness and fatigue caused by both the disease and treatment [43]. Cruzado et al. [4] and Vardy et al. [5] demonstrated that more than one-third of the patients experience substantial cognitive impairment just after a colorectal cancer diagnosis but prior to chemotherapy. Furthermore, undergoing surgery or local therapy before chemotherapy may act as a confounding variable in the measurement of cognitive impairment [44]. Our results of the subsidiary analysis show the effects of different cancer treatments on cognitive function. Three studies included in the subsidiary analysis measured the neurocognitive functions of rectal cancer patients before and after neoadjuvant chemoradiation therapy. Two prospective studies out of the three included had 324 rectal cancer patients of the Dutch multicenter Prospective Data Collection Initiative on Colorectal Cancer (PLCRC) cohort [19] and 29 patients with mid-to-distal rectal cancer from the Institute of Cancer of the State of Sao Paublo [20] who underwent surgery, such as total mesorectal excision with abdominoperineal resection or lower anterior resection, between measurements. The maximal treatment interventions had a moderate effect size (SMD, –0.374; 95% CI, –0.494 to –0.25; $p < 0.001$) on subjective cognitive impairment. This is in contrast to our main analysis, which only examined the effects of chemotherapy. Therefore, neurocognitive deficits experienced by cancer patients can result not only from chemotherapy but also from a multitude of factors involved in the course of treatment.

In addition, there are notable differences in the results between colorectal cancer and breast cancer patients. This may be due to differences in chemotherapy regimens. Breast cancer regimens generally consist of anthracyclines (doxorubicin, epirubicin) and/or taxanes (paclitaxel, docetaxel) [45]. In contrast, colorectal cancer chemotherapy regimens mainly consist of 5-FU and oxaliplatin [6]. Although 5-FU and oxaliplatin, used individually or in combination, may cause several cognitive impairments including memory deficits in rodent models [8,46,47], our results suggest that this effect may be minimal in humans.

A novel finding from our systematic review is that age can act as an important moderator in the relationship between chemotherapy and cognitive function. Research studies have consistently shown that only a subgroup of patients showed chemotherapy-induced cognitive impairment. This effect has been associated with age, cognitive functioning, and premorbid cognitive impairment [48]. Older breast cancer patients with lower baseline cognitive reserves showed

diminished performance in processing speed and verbal ability domains when exposed to chemotherapy [11]. Our finding that age is negatively associated with the degree of cognitive impairment supports the hypothesis that age may be a characteristic factor of the vulnerable subgroup. As previous meta-analyses did not identify an association between age and chemotherapy-induced cognitive impairment [3,28-34], we believe that our findings can address this knowledge gap.

Though several mechanisms associated with chemotherapy-induced cognitive impairment have been suggested, our results support the "accelerated aging hypothesis," which posits that chemotherapy leads to early onset frailty, and patients who undergo chemotherapy show a steeper decline in cognitive function [43,49]. Chemotherapy accelerates the shortening of telomeres and has long-term implications, including the accumulation of DNA damage or free-radical damage and an overall decline in immune/neuroendocrine function [49,50]. These aging-related biological factors are also risk factors for dementia and other neurodegenerative diseases.

Our meta-analyses were conducted on longitudinal studies in order to measure the effect of chemotherapy exclusively [42]. Applying the SMD method which calculated the baseline and shortest follow-up results supports this intention. We were also able to merge the results of cognitive function tests based on various subgroups with overall cognitive function. This allowed us to compare the results of objective vs. subjective cognitive function, objective cognitive function in various cognitive domains, and the main analyses with the pooled results of a separate group comprised of rectal cancer patients receiving neoadjuvant chemotherapy. Lastly, to identify the cause of heterogeneity, we were able to demonstrate the relationship between age and cognitive impairment through a separate meta-regression analysis.

However, we are aware of several limitations of this study. As discussed above, most of the studies included in the analyses did not consider the practice effects associated with the assessments. Tests on cognitive functions are more susceptible to practice effects especially when test-retest intervals are short [51]. Additionally, it was difficult to estimate the differences in cognitive effect by chemotherapy regimen, since studies we have reviewed did not distinguish the effects of each chemotherapy regimen. Although we standardized the effect sizes by estimating the SMDs, caution is required while interpreting such results.

In conclusion, results from our meta-analyses did not show profound evidence supporting cognitive decline after chemotherapy in colorectal cancer patients in general, but we were able to detect the vulnerability of the older colorectal cancer patients to cognitive decline after cancer treatment. Our findings also suggest that providing preventive measures and rehabilitation programs for high-risk patients can reduce the cognitive risks of chemotherapy in colorectal cancer [9,10]. We believe that our findings provide a valuable perspective on "chemo-brain" in colorectal cancer patients. Further investigation is needed to verify the effect of chemotherapy in each cognitive domain and the relationship between age and chemotherapy-induced cognitive impairment.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The Institutional review board (IRB) of Yonsei University Health System advised that a systematic review and meta-analysis do not need to be reviewed and approved. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration.

Author Contributions

Conceived and designed the analysis: Hwang SY, Jung SJ.
Collected the data: Hwang SY, Ha B, Lee D, Kim S, Ryu S, Yang J, Jung SJ.
Contributed data or analysis tools: Kim K.
Performed the analysis: Kim K.
Wrote the paper: Hwang SY, Kim K, Jung SJ.
Reviewed the draft: Hwang SY, Kim K, Ha B, Lee D, Kim S, Ryu S, Yang J, Jung SJ.
Obtained funding: Jung SJ.
Administrative, technical, or material support: Yang J.
Study supervision: Jung SJ.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
2. van Dam FS, Schagen SB, Muller MJ, Boogerd W, vd Wall E, Droogleever Fortuyn ME, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst. 1998;90:210-8.
3. Anderson-Hanley C, Sherman ML, Riggs R, Agocha VB, Compas BE. Neuropsychological effects of treatments for adults with cancer: a meta-analysis and review of the literature. J Int Neuropsychol Soc. 2003;9:967-82.
4. Cruzado JA, Lopez-Santiago S, Martinez-Marin V, Jose-Moreno G, Custodio AB, Feliu J. Longitudinal study of cognitive dysfunctions induced by adjuvant chemotherapy in colon cancer patients. Support Care Cancer. 2014;22:1815-23.
5. Vardy JL, Dhillon HM, Pond GR, Rourke SB, Bekele T, Renton C, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. J Clin Oncol. 2015;33:4085-92.
6. Seigers R, Fardell JE. Neurobiological basis of chemotherapy-induced cognitive impairment: a review of rodent research. Neurosci Biobehav Rev. 2011;35:729-41.
7. Branca JJ, Maresca M, Morucci G, Becatti M, Paternostro F, Gulisano M, et al. Oxaliplatin-induced blood brain barrier loosening: a new point of view on chemotherapy-induced neurotoxicity. Oncotarget. 2018;9:23426-38.
8. Wigmore PM, Mustafa S, El-Beltagy M, Lyons L, Umka J, Bennett G. Effects of 5-FU. Adv Exp Med Biol. 2010;678:157-64.
9. Vardy JL, Bray VJ, Dhillon HM. Cancer-induced cognitive impairment: practical solutions to reduce and manage the challenge. Future Oncol. 2017;13:767-71.
10. Fernandes HA, Richard NM, Edelstein K. Cognitive rehabilitation for cancer-related cognitive dysfunction: a systematic review. Support Care Cancer. 2019;27:3253-79.
11. Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol. 2010;28:4434-40.
12. Bleecker ML, Ford DP, Celio MA, Vaughan CG, Lindgren KN. Impact of cognitive reserve on the relationship of lead exposure and neurobehavioral performance. Neurology. 2007;69:470-6.
13. Anstey KJ, Sargent-Cox K, Cherbuin N, Sachdev PS. Self-reported history of chemotherapy and cognitive decline in adults aged 60 and older: the PATH Through Life Project. J Gerontol A Biol Sci Med Sci. 2015;70:729-35.
14. Lee SH, Lee TG, Baek MJ, Kim JJ, Park SS, Lee SJ. Quality of life changes during adjuvant chemotherapy in patients with colon cancer. Korean J Clin Oncol. 2016;12:60-6.
15. Andreis F, Ferri M, Mazzocchi M, Meriggi F, Rizzi A, Rota L, et al. Lack of a chemobrain effect for adjuvant FOLFOX chemotherapy in colon cancer patients: a pilot study. Support Care Cancer. 2013;21:583-90.
16. Sales MV, Suemoto CK, Apolinario D, Serrao V, Andrade CS, Conceicao DM, et al. Effects of adjuvant chemotherapy on cognitive function of patients eith rarly-stage volorectal vancer. Clin Colorectal Cancer. 2019;18:19-27.
17. Mayrbaurl B, Giesinger JM, Burgstaller S, Piringer G, Holzner B, Thaler J. Quality of life across chemotherapy lines in patients with advanced colorectal cancer: a prospective single-center observational study. Support Care Cancer. 2016;24:667-74.
18. Tsunoda A, Nakao K, Watanabe M, Matsui N, Tsunoda Y. Health-related quality of life in patients with colorectal cancer who receive oral uracil and tegafur plus leucovorin. Jpn J Clin Oncol. 2010;40:412-9.
19. Couwenberg AM, Burbach JP, van Grevenstein WM, Smits AB, Consten EC, Schiphorst AH, et al. Effect of neoadjuvant therapy and rectal surgery on health-related quality of life in patients with rectal cancer during the first 2 years after diagnosis. Clin Colorectal Cancer. 2018;17:e499-512.
20. Souza J, Nahas CS, Nahas SC, Marques CF, Ribeiro Junior U, Cecconello I. Health-related quality of life assessment in patients with rectal cancer treated with curative intent. Arq Gastroenterol. 2018;55:154-9.
21. Bencova V, Krajcovicova I, Svec J. Indication of pre-surgical radiochemotherapy enhances psychosocial morbidity among patients with resectable locally advanced rectal cancer. Neoplasma. 2016;63:635-41.
22. Horowitz TS, Trevino M, Gooch IM, Duffy KA. Understanding the profile of cancer-related cognitive impairments: a critique of meta-analyses. J Natl Cancer Inst. 2019;111:1009-15.
23. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 scoring manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
25. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa, ON: Ottawa Hospital Research Institute; 2021 [cited 2021 Feb 9]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
26. Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: advantages and limitations of the Newcastle Ottawa Scale. World J Meta-Anal. 2017;5:80-4.
27. Faraone SV. Interpreting estimates of treatment effects: implications for managed care. P T. 2008;33:700-11.
28. Hodgson KD, Hutchinson AD, Wilson CJ, Nettelbeck T. A meta-analysis of the effects of chemotherapy on cognition in patients with cancer. Cancer Treat Rev. 2013;39:297-304.
29. Bernstein LJ, McCreath GA, Komeylian Z, Rich JB. Cognitive impairment in breast cancer survivors treated with chemotherapy depends on control group type and cognitive

domains assessed: a multilevel meta-analysis. Neurosci Biobehav Rev. 2017;83:417-28.
30. Jansen CE, Miaskowski C, Dodd M, Dowling G, Kramer J. A metaanalysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. Cancer. 2005;104:2222-33.
31. Falleti MG, Sanfilippo A, Maruff P, Weih L, Phillips KA. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. Brain Cogn. 2005;59:60-70.
32. Stewart A, Bielajew C, Collins B, Parkinson M, Tomiak E. A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. Clin Neuropsychol. 2006;20:76-89.
33. Ono M, Ogilvie JM, Wilson JS, Green HJ, Chambers SK, Ownsworth T, et al. A meta-analysis of cognitive impairment and decline associated with adjuvant chemotherapy in women with breast cancer. Front Oncol. 2015;5:59.
34. Jim HS, Phillips KM, Chait S, Faul LA, Popa MA, Lee YH, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012;30:3578-87.
35. Lindner OC, Phillips B, McCabe MG, Mayes A, Wearden A, Varese F, et al. A meta-analysis of cognitive impairment following adult cancer chemotherapy. Neuropsychology. 2014;28:726-40.
36. Bartels C, Wegrzyn M, Wiedl A, Ackermann V, Ehrenreich H. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC Neurosci. 2010;11:118.
37. Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. Neuropsychological assessment. 4th ed. New York: Oxford University Press; 2004.
38. McCaffrey RJ, Duff K, Westervelt HJ. Practitioner's guide to evaluating change with neuropsychological assessment instruments. New York: Springer Science & Business Media; 2000.
39. McCaffrey RJ, Westervelt HJ. Issues associated with repeated neuropsychological assessments. Neuropsychol Rev. 1995;5:203-21.
40. Dodge HH, Zhu J, Lee CW, Chang CC, Ganguli M. Cohort effects in age-associated cognitive trajectories. J Gerontol A Biol Sci Med Sci. 2014;69:687-94.
41. Dodge HH, Zhu J, Hughes TF, Snitz BE, Chang CH, Jacobsen EP, et al. Cohort effects in verbal memory function and practice effects: a population-based study. Int Psychogeriatr. 2017;29:137-48.
42. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011;12:703-8.
43. Pendergrass JC, Targum SD, Harrison JE. Cognitive impairment associated with cancer: a brief review. Innov Clin Neurosci. 2018;15:36-44.
44. Hardy SJ, Krull KR, Wefel JS, Janelsins M. Cognitive changes in cancer survivors. Am Soc Clin Oncol Educ Book. 2018;38:795-806.
45. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. BMC Med. 2015;13:195.
46. Bianchi E, Di Cesare Mannelli L, Micheli L, Farzad M, Agliano M, Ghelardini C. Apoptotic process induced by oxaliplatin in rat hippocampus causes memory impairment. Basic Clin Pharmacol Toxicol. 2017;120:14-21.
47. Fardell JE, Vardy J, Shah JD, Johnston IN. Cognitive impairments caused by oxaliplatin and 5-fluorouracil chemotherapy are ameliorated by physical activity. Psychopharmacology (Berl). 2012;220:183-93.
48. Vega JN, Dumas J, Newhouse PA. Cognitive effects of chemotherapy and cancer-related treatments in older adults. Am J Geriatr Psychiatry. 2017;25:1415-26.
49. Maccormick RE. Possible acceleration of aging by adjuvant chemotherapy: a cause of early onset frailty? Med Hypotheses. 2006;67:212-5.
50. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer. 2007;7:192-201.
51. Dikmen SS, Heaton RK, Grant I, Temkin NR. Test-retest reliability and practice effects of expanded Halstead-Reitan Neuropsychological Test Battery. J Int Neuropsychol Soc. 1999;5:346-56.