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

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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...
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 Systematic 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]...
was newly included by manual search, resulting in a total of 11 studies. 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. 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 were 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 neurologi- cal 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 I² statistics were calculated to evaluate the heterogeneity in the included studies. 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. 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. 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. 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study designe</th>
<th>No. of initial participants</th>
<th>Follow-up period (mo)</th>
<th>Age (yr), mean±SD or median (range)</th>
<th>Male, n (%)</th>
<th>Education (yr)</th>
<th>Cancer site</th>
<th>Cancer stage</th>
<th>Chemotherapy regimen</th>
<th>Neuropsychological measurement</th>
<th>Covariates</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreis et al. (2013) [15]</td>
<td>Prospective study</td>
<td>47$^{a)}$</td>
<td>6</td>
<td>58.68±9.62 (34.04)</td>
<td>16 (34.04)</td>
<td>9.43 (3.91)</td>
<td>Colon (47)</td>
<td>3 (47)</td>
<td>FOLFOX4</td>
<td>Clock Drawing Test, Rey Auditory Verbal Learning Test (call/recall), Rey Complex Figure, (copy/recall)</td>
<td>Age, education, sex</td>
<td>7</td>
</tr>
<tr>
<td>Vardy et al. (2019) [5] (localized)</td>
<td>Prospective study</td>
<td>173</td>
<td>6</td>
<td>57.0 (23-75)</td>
<td>117 (67.63)</td>
<td>13.8 (3.3)</td>
<td>Colon (104), rectum (66)</td>
<td>1 (2), 2 (46), 3 (125)</td>
<td>Adjuvant (123), neoadjuvant (46), unknown (4)</td>
<td>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)</td>
<td>Age, sex, education, time between assessments, practice effect</td>
<td>9</td>
</tr>
<tr>
<td>Vardy et al. (2015) [5] (metastatic)</td>
<td>Prospective study</td>
<td>73</td>
<td>6</td>
<td>55.5 (28-75)</td>
<td>40 (54.79)</td>
<td>13.7 (3.4)</td>
<td>Colon (54), rectum (16)</td>
<td>3 (4), 4 (69)</td>
<td>None (1), FU (4), oxaliplatin (36), chemoradiation (2), irinotecan (20), other (2), missing (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of initial participants</th>
<th>Follow-up period (mo)</th>
<th>Age (yr), mean±SD or median (range)</th>
<th>Male, n (%)</th>
<th>Education (yr)</th>
<th>Cancer site</th>
<th>Cancer stage</th>
<th>Chemotherapy regimen</th>
<th>Neuropsychological measurement</th>
<th>Covariates</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruzado et al. (2014) [4]</td>
<td>Prospective study</td>
<td>81</td>
<td>6</td>
<td>66.96±9.52 (61.73) (4.1)</td>
<td>50</td>
<td>6.9</td>
<td>-</td>
<td>1 (28), Oxaliplatin plus 5-FU / leucovorin (FOLFOX4) adjuvant CT regimen within 6 to 8 weeks post-surgery</td>
<td>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</td>
<td>Age, sex, education</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sales et al. (2019) [16]</td>
<td>Prospective study</td>
<td>47</td>
<td>12</td>
<td>61.1±8.8 (63.83) (3.9)</td>
<td>30</td>
<td>7.9</td>
<td>-</td>
<td>2 (23), 6 cycles (6 mo) of 5-FU, leucovorin with or without oxaliplatin</td>
<td>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</td>
<td>Age, sex, education, depressive symptoms at baseline</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Anstey et al. (2015) [13]</td>
<td>Prospective study</td>
<td>20</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>TMT A, TMT B, Unadjusted^2)</td>
<td>California Verbal Learning Test (Immediate / Delayed), Symbol-Digit-Modality test, Simple / choice reaction time, Verbal Fluency (F words, A words)</td>
<td>Age, sex, education</td>
<td>6</td>
</tr>
</tbody>
</table>

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Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of initial participants</th>
<th>Follow-up period (mo)</th>
<th>Age (yr), mean±SD or median (range)</th>
<th>Male (n)</th>
<th>Education</th>
<th>Cancer site</th>
<th>Cancer stage</th>
<th>Chemotherapy regimen</th>
<th>Neuropsychological measurement</th>
<th>Covariates</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayrbaurl et al. (2016) [17]</td>
<td>Prospective study</td>
<td>100</td>
<td>3 cycles</td>
<td>66.4±10.6</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>Advanced colorectal cancer</td>
<td>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%)</td>
<td>EORTC-QLQ C30 Cognitive functioning</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Lee et al. (2016) [14]</td>
<td>Prospective study</td>
<td>56</td>
<td>6 cycles</td>
<td>59.5±11.5</td>
<td>31 (55.36)</td>
<td>None 8 elementary school 17 middle school 10 high school 11 college or more 10 (people)</td>
<td>Rectal (56)</td>
<td>2 (16), 3 (40), 4 (9)</td>
<td>6 cycles of FOLFOX</td>
<td>EORTC-QLQ C30 Cognitive functioning</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

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Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Study designe</th>
<th>No. of initial participants</th>
<th>Follow-up period (mo)</th>
<th>Age (yr), mean±SD or median (range)</th>
<th>Male, n (%)</th>
<th>Education (yr)</th>
<th>Cancer site</th>
<th>Cancer stage</th>
<th>Chemotherapy regimen</th>
<th>Neuropsychological measurement</th>
<th>Covariates</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsunoda et al. (2010) [18]</td>
<td>Prospective study</td>
<td>99</td>
<td>7</td>
<td>65±10</td>
<td>58 (58.59)</td>
<td>-</td>
<td>Colon (59), rectal (40)</td>
<td>2 (49), 3 (50)</td>
<td>Oral uracil/tegafur dose 300 mg/m²/day, oral leucovorin dose of 75 mg/day on days 1-28, followed by a 7-day rest (35 days/cycle ×5 cycles)</td>
<td>EORTC-QLQ C30 Cognitive functioning</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Couwenberg et al. (2018) (LAR) [19]</td>
<td>Prospective study</td>
<td>134</td>
<td>3</td>
<td>64 (38-83)</td>
<td>93 (69.4)</td>
<td>-</td>
<td>Rectal (134)</td>
<td>-</td>
<td>cT2 (16), cT3 (104), cT4 (14), cN0 (16), cN1 (55), cN2 (63), cM0 (121), cM1 (12), M stage unknown (1)</td>
<td>EORTC-QLQ C30 Cognitive functioning</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Couwenberg et al. (2018) (APR) [19]</td>
<td>Prospective study</td>
<td>119</td>
<td>3</td>
<td>66 (26-87)</td>
<td>91 (76.5)</td>
<td>-</td>
<td>Rectal (119)</td>
<td>-</td>
<td>cT1 (1), cT2 (15), cT3 (83), cT4 (20), cN0 (21), cN1 (51), cN2 (47), cM0 (113), cM1 (4), M stage unknown (2)</td>
<td>EORTC-QLQ C30 Cognitive functioning</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(Continued to the next page)
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/FOLFIRI. 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 with 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. (7 months). There was no apparent association between follow-up period and effect size ($\beta$=-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 ($I^2=60\%$).

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,
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 ($\beta$=−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, 0.000; 95% CI, −0.093 to 0.093) (S4 Fig.). Meta-regression from this scenario was also similar to that of main analysis ($\beta$=−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

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

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

CI, confidence interval; SMD, standardized mean difference. $^a$One cycle = one month in average.
CANCER RESEARCH AND TREATMENT

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].

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.
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, 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

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

CI, confidence interval; SMD, standardized mean difference.

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

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

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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.

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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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