CHANGES IN SUBJECTIVE MEASURES OF COGNITIVE FUNCTION IN OLDER ADULTS FROM THE INITIATION THROUGH 12 MONTHS AFTER THE RECEIPT OF CHEMOTHERAPY

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Abstract

Background: Cognitive impairment has a negative impact on older patients with cancer.

Objective: Evaluate for inter-individual differences in two subjective measures of cognitive function in older patients (n = 112), as well as determine which demographic, clinical, and symptom characteristics, and levels of physical function, were associated with initial levels and with the trajectory of each of these two measures.

Methods: Cognitive function was assessed using the cognitive function scale from the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (QLQ-C30 CF) and the Attentional Function Index (AFI) at the initiation of chemotherapy and at 1, 3, 6, 9, and 12 months after its initiation. Hierarchical linear modeling was used to assess for inter-individual differences in and characteristics associated with initial levels and changes in cognitive function.

Results: Characteristics associated with decreases in QLQ-C30 CF scores at the initiation of chemotherapy were longer time since the cancer diagnosis and higher depression scores. Characteristics associated with poorer AFI scores at enrollment were lower levels of education and higher depression scores. No characteristics were associated with worse trajectories of either cognitive function measure.

Conclusions: Some older patients undergoing chemotherapy experience decrements in cognitive function.

Implication for practice: Our findings suggest that clinicians need to assess for depressive symptoms in older patients prior to the initiation of chemotherapy. Evidence-based interventions

(e.g., cognitive stimulation, increased physical activity) can be recommended to maintain and increase cognitive function in older oncology patients.

INTRODUCTION

Cancer-related cognitive impairment (CRCI) occurs in 12% to 75% of patients receiving chemotherapy.[1] By 2035, almost 60% of all new cancer cases worldwide will occur in adults ≥65 years of age[2] and recent evidence suggests that compared to healthy controls, older oncology patients undergoing chemotherapy experience a greater decline in cognitive function.[3, 4] Older adults may be more vulnerable to CRCI because the cancer itself and associated treatments may accelerate the neurodegenerative changes that often occur with aging.[3-8]

While chemotherapy is a common treatment for older oncology patients, only seven longitudinal studies have evaluated for changes in CRCI in the elderly.[6, 9-14] Across these studies, findings regarding overall changes in cognitive function are inconclusive. In three of these studies,[9-11] 36% to 51% of the patients had a decline in cognitive function. However, in three studies,[6, 12, 13] cognitive function was stable for the majority of the patients, and in one study cognitive function improved over time.[14] However, across these studies, a large amount of inter-individual variability in changes in cognitive function was noted. Some of these inconsistent findings may be related to differences in the measures that were used to evaluate cognitive function. Specifically, three used only self-report,[6, 9, 12] two used only objective,[10, 13] and two used both self-report and objective [11, 14] measures.

While neuropsychological tests are considered the gold standard for the assessment of cognitive impairment, these tests are not always feasible or affordable.[15] Therefore, self-reports of perceived changes in cognitive function are equally important in the context of patient-reported outcome research.[16, 17] However, it is interesting to note that in the three studies that evaluated cognitive function using a self-report measure,[6, 9, 12] the findings were inconsistent. In the first study of

older breast cancer patients (i.e., ≥65 years of age; n=45),[9] that evaluated cognitive function using the Squire Memory Self-Rating Questionnaire,[18] 51% of the older adults perceived a decline in memory from before to 6 months after treatment. In the second study of older breast cancer patients (n=297), that evaluated cognitive function using an investigator-developed self-report measure,[6] no changes in cognitive function were found from prior to through two years after treatment. In another study of older breast cancer patients (n=1280),[12] that used the cognitive function scale from the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30 CF),[19] 92% of the patients had no decline from the initiation of through seven years after treatment. Only 7.6% of patients reported accelerated cognitive decline.

While the Squire Memory Self-Rating Questionnaire assesses memory and the two items from the QLQ-C30 assess memory and concentration, none of these studies evaluated an older patient's ability to direct attention towards planning, decision-making, and abstract thinking that are of particular importance to older adults. In addition, only patients with breast cancer were included in these studies; the number of assessments in the first year following chemotherapy was limited to a maximum of three; and none of them evaluated for factors that contributed to inter-individual variability in self-reported changes in cognitive function.

A number of demographic (i.e., increased age, female gender, lower level of education),[1, 20, 21] clinical (i.e., higher level of comorbidity, lower functional status),[1, 20] and symptom (i.e., higher levels of anxiety, depression, fatigue, pain, sleep disturbance) [1, 20] characteristics have been associated with decrements in cognitive function. Only one of these studies evaluated pretreatment symptoms (i.e., depression, anxiety, fatigue, sleep, pain) as risk factors for CRCI in older breast

cancer patients.[14] Higher levels of these symptoms at diagnosis were associated with cognitive deficits in the first 24 months after diagnosis. However, no studies have evaluated a comprehensive set of demographic, clinical, and symptom characteristics as risk factors for CRCI at the initiation of and for 12 months following chemotherapy. As noted in one study,[12] additional research is needed to determine the factors that place older patients at increased risk for CRCI.

While an accumulating body of evidence from the geriatric literature suggests that decrements in cognitive function and physical function are highly related and often co-occur as people age,[22-28] only one of the studies cited above evaluated for associations between cognitive and physical function in older patients receiving chemotherapy.[12] In this study, three groups of patients with different trajectories of cognitive function were identified. The maintaining high group (42.4%) began with nearly perfect scores on QLQ-C30 CF and maintained this level for seven years. The phase shift group (50.1%) shifted slightly below and maintained this level in parallel with the maintaining high group. In contrast, the accelerated decline group (7.6%) had low baseline QLQ-C30 CF scores and steeper rate of decline. Higher premorbid physical function decreased the odds of being in the phase shift or accelerated decline groups versus the maintaining high group. However, for a number of the patients, the baseline assessment was done mid-treatment. As noted in three reviews,[1, 29, 30] longitudinal studies of changes in and factors associated with decrements in cognitive function in older adults receiving chemotherapy are urgently needed to inform clinical decisions and follow-up care.

In our previous report,[31] we found that the scores for two subjective measures of cognitive function, namely the QLQ-C30 CF and Attentional Function Index (AFI) [32] while conceptually related were only moderately correlated (r = .57, p<.001). This

finding suggests that these two scales evaluate distinct, but related, aspects of cognitive function. Based on our findings, we hypothesize that common and distinct risk factors will be associated with changes in QLQ-C30 CF and AFI scores in older oncology patients.

Therefore, the purposes of this longitudinal study, in a sample of older oncology patients who were followed from the initiation of through 12 months after the administration of chemotherapy (n=112), were to: evaluate for inter-individual differences in two subjective measures of cognitive function (i.e., QLQ-C30 CF, AFI [32]) and to determine which demographic, clinical, and symptom characteristics, as well as subjective and objective measures of physical function, were associated with initial levels as well as with the trajectories of each of these subjective measures.

METHODS

Sample and Settings

This analysis is part of a longitudinal study of changes in cognitive and physical function in older cancer patients receiving chemotherapy whose methods are published elsewhere.[33] In brief, eligible patients were ≥60 years of age; had a diagnosis of gynecological or colorectal cancer; were scheduled to receive primary or adjuvant chemotherapy; had a Montreal Cognitive Assessment (MoCA) score of ≥23 [34]; and had a Karnofsky Performance Status (KPS) score of ≥60.[35] A total of 208 patients were approached and 149 consented to participate (71.6% response rate). Of these 149 patients, one withdrew and nine were excluded because they had a MoCA score of <23. A total of 139 patients were enrolled into this study. For this longitudinal study, complete data from 112 patients were available to perform the hierarchical linear modeling (HLM) analysis.

Instruments

Demographic and clinical characteristics - Patients completed a demographic questionnaire, the KPS scale,[36, 37] and the Self-Administered Comorbidity Questionnaire (SCQ-16).[38] The SCQ-16 evaluates the occurrence of, treatments for, and functional impact of 16 common comorbid conditions. Total SCQ scores can range from 0 to 48.

Subjective measures of cognitive function - The QLQ-C30 CF scale [19] and the AFI [32] were the self-report measures of cognitive function used in the study.

The QLQ-C30 CF scale consists of two items (i.e., Have you had difficulty in concentrating on things, like reading a newspaper or watching television?; Have you had difficulty remembering things?). The questions have a 1-week time frame and use a four-point response format (“not at all,’’ “a little,’’ “quite a bit,’’ and “very much’’). The raw scores were linearly transformed to a 0 to 100 scale, using the algorithm in the QLQ-C30 scoring manual.[39] Higher scores indicate a better level of cognitive function.

The 16-item AFI assesses an individual’s perceived effectiveness in performing daily activities that are supported by attention and working memory.[32, 40] Each item was rated on a 0 to 10 numeric rating scale and a total score was calculated as the mean of the 16 items. A higher total AFI score indicates greater capacity to direct attention.[32] Total scores are grouped into three categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function).[41] The AFI has well established validity and reliability.[32] In the current study, its Cronbach's alpha was 0.93.

Symptom measures - The 20-item Center for Epidemiological Studies-Depression (CES-D) scale was used to evaluate depressive symptoms.[42] Total score can range from 0 to 60, with scores of $\geq$16 indicating the need for individuals to seek

clinical evaluation for depression. In the current study, the Cronbach's alpha for the CES-D total score was 0.84.

Additional symptoms were evaluated using the QLQ-C30 that consists of eight symptom scales (i.e., fatigue (3 items), pain (2 items), nausea and vomiting (2 items), dyspnea (1 item), insomnia (1 item), appetite loss (1 item), constipation (1 item), diarrhea (1 item)).[19] The questions have a 1-week time frame and use a four-point response format ("not at all", "a little'', "quite a bit", and "very much''). The raw scores were linearly transformed to a 0 to 100 scale, using the algorithm in the QLQ-C30 scoring manual.[39] Higher scores indicate more severe symptoms. In this study, the Cronbach`s alpha for the fatigue subscale that had more than 2 items was 0.90.

Subjective measures of physical function - The physical function and role functions scales from the QLQ-C30 [19] were the self-report measures of physical function used in the study. The physical function scale consists of five items (i.e., Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? Do you have any trouble taking a long walk? Do you have any trouble taking a short walk outside of the house? Do you need to stay in bed or a chair during the day? Do you need help with eating, dressing, washing yourself, or using the toilet?). The role function scale consists of two items (i.e., Were you limited in doing either your work or other daily activities? Were you limited in pursuing your hobbies or other leisure time activities?). The questions have a 1-week time frame and use a four-point response format ("not at all,'' "a little,'' "quite a bit,'' and "very much''). The raw scores were linearly transformed to a 0 to 100 scale, using the algorithm in the QLQ-C30 scoring manual.[39] Higher scores indicate a better level of function. In this study, the Cronbach`s alpha for the physical function subscale was 0.78.

Objective measures of physical function – The gait speed and repeated chair stand tests from the Short Physical Performance Battery (SPPB) [43] were the objective measures of physical function used in this study. Depending on the available space to perform the test, gait speed was scored based on the time taken to walk 3 or 4 meters at usual speed. The test was performed twice and the shortest time was used in the analysis. Tape was used to mark out the distance on a flat unobstructed course. Patients began in a standing position, with their toes just touching the start line. The timer was started when the patients began moving and was stopped when the patients' foot completely crossed the 3- or 4-meter line. Completion times of <3.62 or <4.82 seconds (i.e., 1.2 meter/second (m/sec)), respectively are considered normal.[43]

The repeated chair stand task was scored as the time taken to complete 5 repetitions of the sit to stand maneuver. All sit-to-stand maneuvers were performed using a dining chair. Patients were instructed to fold their arms across their chest during the task. The timer was started when the patients' back left the backrest and was stopped when they straightened out completely for the fifth time. A completion time of $\leq$11.19 sec is considered normal.[43]

Study Procedures

Regional Committee for Medical and Research Ethics, Norway and the Institutional Review Board at each of the study sites approved the study (reference No. 2015/1277/REC South East). Oncologists or nurses approached patients prior to the initiation of chemotherapy to assess their interest in study participation. Written informed consent was obtained from all patients. Patients completed study questionnaires and the performance tests in their homes or in the clinic, a total of six times over one year (i.e., at the initiation of chemotherapy administration and

approximately one, three, six, nine, and twelve months after its initiation.). Reliability testing for all of the study measures was done on an annual basis with all of the research staff. An inter-rater reliability of >.90 was achieved for all of the study measures.

Statistical Analyses

Descriptive statistics and frequency distributions were generated for demographic and clinical characteristics, symptom severity scores, and measures of cognitive function and physical function using SPSS version 27.[44] Subjective measures of cognitive function (i.e., QLQ-C30 CF, AFI) were assessed at the initiation of chemotherapy and at one, three, six, nine, and twelve months after its initiation. All of the other demographic, clinical, and symptom characteristics, as well as the function measures that were evaluated as predictors in the HLM analysis were assessed at the initiation of chemotherapy.

HLM based on full maximum likelihood estimation was done using the software developed by Raudenbush and colleagues.[45, 46] Separate HLM analyses were done for the QLQ-C30 CF and AFI. During stage 1, intra-individual variability in the scores for each measure over time was examined. At this point, the model was constrained to be unconditional and likelihood ratio tests were used to determine the best fitting model.

The second stage of HLM analysis examined inter-individual differences in the trajectories of each of the measure's scores by modeling the individual change parameters as a function of proposed predictors at level 2. Supplemental Tables 1 and 2 present the list of the proposed predictors for the QLQ-C30 CF and AFI, respectively, that was developed based on a literature review on CRCI in older oncology patients.[1, 14, 20, 21]

To improve estimation efficiency and construct a parsimonious model, an exploratory level 2 analysis was completed in which each potential predictor was assessed to determine whether it would result in a better model if it alone were added as a level 2 predictor. Predictors with a t-value of <2.0 were dropped from subsequent model testing. All potential significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other variables were retained in the final model. A p-value of <.05 indicated statistical significance.

RESULTS

Patient Characteristics

As described in our previous publication,[47] the demographic and clinical characteristics, as well as the symptom severity scores and scores for the measures of physical function for the sample (n=112) are summarized in Table 1. Patients were 70.4 (±6.5) years of age, well-educated (83.9% high school or higher), and were diagnosed with either gynecological (90.2%) or colorectal (9.8%) cancer. Most patients were female (93.8%), married (64.3%), and were not employed (83.0%). Mean number of comorbidities was 2.0 (±1.7) and mean SCQ score was 3.8 (±3.8). On average, the patients were 1.3 (±3.9) years from their cancer diagnosis, had metastatic disease (78.6%), and had surgery prior to chemotherapy (54.5%).

At enrollment, the mean CES-D score (11.6 ± 8.2) was below the clinically meaningful cutoff score of ≥16. The mean QLQ-C30 symptom scores ranged from 8.0 (±15.2) for nausea and vomiting to 43.9 (±26.3) for fatigue. While the enrollment score of 13.4 (±5.5) sec for the chair stand test suggests a lower level of physical function, the gait speed score (0.94±0.26sec) suggests a normal level of PF. The

mean QLQ-C30 physical function and role function scores were 69.2 (±21.5) and 60.7 (±31.5), respectively (Table1).

Individual and mean change in QLQ-C30 CF scores

First stage of HLM analysis examined how QLQ-C30 CF scores changed from the initiation of through 12 months after chemotherapy administration. Because the quadratic model had no covariates, the intercept represents the estimated QLQ-C30 CF score (i.e., 86.542 on a 0 to 100 scale) at the initiation of chemotherapy. Estimated linear rate of change in the QLQ-C30 cognitive function score, for each additional assessment, was -1.314 ($p<.01$) and estimated quadratic change was .095 ($p<.05$, Table 2).

Figure 1A displays the trajectory for the QLQ-C30 CF score from the initiation of through 12 months after chemotherapy administration. QLQ-C30 CF scores decreased slightly until month 6 and then increased slightly from month 6 to month 12. While these results indicate a sample-wide change in QLQ-C30 CF scores over time, as illustrated in Figure 1B and by the variance components (Table 2) a considerable amount of inter-individual variability existed in the trajectories of the QLQ-C30 CF scores. These results supported additional analyses of predictors of inter-individual differences in initial levels, as well as in the trajectories of these scores. The mean scores for the various groups depicted in all of the figures are estimated or predicted means based on the HLM analysis.

Inter-individual differences in the trajectories of QLQ-C30 CF scores

As shown in the final model, the characteristics that were associated with inter-individual differences in QLQ-C30 CF scores at the initiation of chemotherapy were: time since diagnosis and depression (Table 2). No characteristic was associated with inter-individual differences in the linear or quadratic slopes for this

measure. Figures 1C and 1D display the adjusted change curves for the QLQ-C30 CF scores that were estimated based on differences in time since diagnosis and depression (i.e., 0 years versus 5 years and lower/higher depression scores calculated based on one standard deviation [SD] below and above the mean CES-D score, respectively). Patients who had a longer time from their diagnosis and patients with higher levels of depressive symptoms were more likely to report lower QLQ-C30 CF scores at enrollment.

Individual and mean change in AFI scores

In terms of AFI scores, because the model had no covariates, the intercept represents the estimated AFI score (i.e., 7.331) at the initiation of chemotherapy (Table 2). As shown in Figure 2A, the AFI scores remained stable from enrollment through month 12. While the results indicate a sample-wide stability in AFI scores over time, as shown in Figure 2B and by the variance components (Table 2), a considerable amount of inter-individual variability existed in the trajectories of AFI scores.

Inter-individual differences in the trajectories of AFI scores

As shown in the final model, the characteristics that were associated with inter-individual differences in AFI scores at the initiation of chemotherapy were education and depression (Table 2). Figures 2C to 2D display the adjusted change curves for the AFI scores that were estimated based on differences in education and depression at enrollment (i.e., primary school vs high school vs college; depression calculated based on one SD below and above the mean CES-D score at enrollment, respectively). Older patients with only a primary school education and those who had higher levels of depressive symptoms had worse AFI scores at the initiation of chemotherapy.

DISCUSSION

This study is the first to evaluate for inter-individual variability in the trajectories of and associated risk factors for decrements in cognitive function in older adults receiving chemotherapy over a twelve month period, using two self-report measures. While the QLQ-C30 CF scale evaluates memory and concentration,[19] the AFI assesses perceived effectiveness in the performance of common activities that require attention and working memory, particularly the ability to formulate plans, carry out tasks, and function effectively in daily life.[32] Our a priori hypothesis that common and distinct characteristics would be associated with decrements in QLQ-C30 CF and AFI scores was supported. Higher depression scores at the initiation of chemotherapy were associated with both of these self-reported measures. However, longer time since diagnosis and lower level of education were distinct characteristics that were associated with lower QLQ-30 CF and worse AFI scores, respectively.

While the enrollment AFI score of our sample was in the moderate range (i.e., 7.3), it is higher than the score (i.e., 6.5) reported for a sample of older patients with heterogenous types of cancer who were evaluated during chemotherapy.[48] In contrast, while our patients' QLQ-C30 CF score was relatively high (i.e., 86.5), it was slightly lower than scores reported by older breast cancer patients (i.e., 92.6) receiving chemotherapy.[12] While mean differences were noted across these studies, the findings suggest that older adults have relatively high levels of cognitive function at the initiation of chemotherapy. However, an alternative explanation is that selection bias occurs in the enrollment of older adults into studies of the effects of chemotherapy on cognitive function.

Consistent with the idea that cognitive function would decline because of increased mental effort needed to compensate for cancer and its treatment,[49] the QLQ-C30 CF scores in our sample decreased to 82.0 at 6 months and then increased to 84.4, at 12 months after the administration of chemotherapy (see Figure 1A). Our finding is consistent with a previous study of older breast cancer patients (i.e., >65 years of age; n=150) that found a small increase in QLQ-C30 CF scores from mid-treatment to 12 months.[50] While these changes in QLQ-C30 CF scores were not clinically meaningful,[51] as noted by Mandelblatt and colleagues,[50] small changes in cognitive function may have a larger impact on older oncology patients who have limited cognitive reserve compared to younger patients.

In contrast to the QLQ-C30 CF scores, AFI scores remained stable from the initiation of through 12 months after the administration of chemotherapy. While the reasons why the trajectories for the two measures are different is not readily apparent, several explanations are plausible. First, since the scores on the two measures cannot be compared directly, it is possible that the AFI captures age-adjusted changes in cognitive function better than QLQ-C30 CF. Alternatively, as noted by Jung and colleagues,[52] the AFI may not capture subtle cognitive changes in a subset of individuals. In addition, it is possible that the QLQ-C30 CF scale that consists of only two items (i.e., Have you had difficulty in concentrating on things, like reading a newspaper or watching television?; Have you had difficulty remembering things?), evaluates relatively concrete but limited aspects of cognitive function.[53] Our findings suggests that these two questions from the EORTC-C30 can be used as a screening tool to evaluate for changes in CRCI in older adults undergoing chemotherapy.

One of the goals of this study was to identify common and distinct characteristics associated with decrements in cognitive function using QLQ-C30 CF and AFI. Depressive symptom scores at enrollment was the only common characteristic. This finding is consistent with our previous report,[54] that found that higher levels of depressive symptoms were associated with a significant decrease in AFI scores in older adults receiving chemotherapy. As shown in Figures 1D and 2D, higher levels of depressive symptoms were associated with clinically meaningful decrements in cognitive function. In our previous [54] and current study, the mean CES-D scores were 10.9 and 11.6, respectively. While these scores are below the clinically meaningful cutoff of $\geq$16, 26.8% of the older patients in the current study reported CES-D scores above this cutoff (i.e., 16 to 42). These findings suggest that clinicians should routinely assess for depressive symptoms in these patients and initiate referrals to psychological services.

Evidence suggests that depression is strongly associated with self-reported cognitive complaints.[12, 20, 55] However, the mechanism that underlies this association is not entirely clear.[56] One plausible explanation is that the biology of cancer (e.g., inflammatory response triggering neurotoxic cytokines) may contribute to both depressive symptoms and lower than expected cognitive performance.[57] It is interesting to note that only one clinical characteristic, namely >5 years since diagnosis, was associated with decrements in QLQ-C30 CF at enrollment. In terms of the AFI, consistent with our previous study,[48] no disease or treatment characteristics were associated with decrements in cognitive function. One plausible explanation for why a longer time since diagnosis was associated with decreases in cognitive function, is that these older adults were exposed to a higher number of cancer treatments. In addition, an interaction may exist between depressive

symptoms and time since diagnosis that should be evaluated in future studies with larger samples.

A lower level of education was the only risk factor associated with decrements in AFI scores at the initiation of chemotherapy. Consistent with previous reports from the older general population,[58, 59] and older oncology patients,[60] we found that compared to older patients with a college education, patients with only a high school and with only a primary school education had progressively worse AFI scores at the initiation of chemotherapy. This finding is supported by previous studies of the general population that found a positive relationship between higher levels of education and higher levels of cognitive function [61] or that higher levels of education were associated with a decrease in the odds of developing cognitive impairment.[62]

It is interesting to note that none of our list of comprehensive demographic, clinical and symptom characteristics were associated with changes in cognitive function over time (i.e., slope predictors). However, these results are consistent with a study of the general population that found few significant predictors of age-related changes in cognitive function.[59] Of note, while neither the subjective or objective measures of physical function were associated with changes in cognitive function, in a previous study of older breast cancer patients,[12] higher levels physical function decreased the odds of long-term cognitive decline and that an accelerated cognitive decline was associated with decrements of physical function. In addition, in our previous study with a different sample,[63] over 50% of the older patients had decrements in physical and cognitive function over two cycles of chemotherapy. Given our relatively small sample size and the known associations between physical and cognitive function,[22, 23, 25, 27, 28] future studies with larger samples need to

evaluate the relative contribution of physical function to changes in cognitive function in older oncology patients.

Practice Implications

The modifiable and non-modifiable characteristics found in this study can be used by oncology nurses to identify older oncology patients who are at increased risk for CRCI during and following chemotherapy and provide early interventions and referrals. While the demographic (e.g., education) and clinical (e.g., ≥5 years since time of diagnosis) characteristics associated with decrements in cognitive function are not modifiable, the one potentially modifiable risk factor (e.g., depression) can be used by oncology nurses to identify patients at risk, monitor them, and initiate appropriate interventions. Our findings suggest that clinicians need to assess for depressive symptoms in older patients prior to the initiation of chemotherapy. Treatment of depression may improve cognitive function before, during, and after treatment. In addition, clinicians can recommend evidence-based interventions like cognitive stimulation and physical activity to maintain cognitive function in this vulnerable population.[64]

LIMITATIONS

Several limitations warrant consideration. Evaluation of cognitive function was limited to self-report questionnaires that primarily evaluated for changes in executive function. Therefore, our findings regarding changes in cognitive function over time, as well as associated risk factors warrant confirmation using objective measures of other domains of cognitive function (e.g., language, social cognition, emotions, visuospatial, and motor functions). Given that the majority of the patients in this study were women with gynecological cancer; were predominantly well educated; and had metastatic disease, our findings may not generalize to all oncology patients.

Despite these limitations, this study is the first to evaluate for changes in cognitive function over a relatively long period of time using two valid, reliable, and commonly used measures. In addition, this study provides new insights into changes in and risk factors for cognitive decline in older adults receiving chemotherapy.

CONCLUSIONS

A large amount of inter-individual variability exists in cognitive function in older oncology patients from the initiation of chemotherapy to one year after treatment. Some older patients undergoing chemotherapy experience decrements in cognitive function.

Figure legends

Figure 1. Trajectory of cognitive function evaluated using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) cognitive function scale from the initiation of through 12 months after the completion of chemotherapy (A). Spaghetti plot of individual cognitive function trajectories for a random sample of 50 patients from the initiation of through 12 months after the completion of (B). Influence of time since diagnosis (C) and depression (D) on interindividual differences in the severity of cognitive function over 12 months.

Figure 2. Trajectory of cognitive function evaluated using the Attentional Function Index (AFI) score from the initiation of through 12 months after the completion of chemotherapy (A). Spaghetti plot of individual attentional function trajectories for a random sample of 50 patients from the initiation of through 12 months after the completion of chemotherapy (B). Influence of education (C) and depression (D) on interindividual differences in the severity of attention function over 12 months.

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Table(s)

Table 1 – Demographic, Clinical, and Symptom Characteristics of the Sample at Enrollment (n=112)

Demographic and clinical characteristics	Mean (SD)
Age (years)	70.4 (6.5)
Time since cancer diagnosis (years)	1.3 (3.9)
Karnofsky Performance Status score	87.1 (10.1)
Body mass index	26.2 (6.3)
Hemoglobin (grams/deciliter)	12.6 (1.7)
Number of cormobid conditions out of 16	2.0 (1.7)
Self-Administered Comorbidity Questionnaire score	3.8 (3.8)
	n (%)
Female gender	105 (93.8)
Education	
Primary school	18 (16.1)
High school	54 (48.2)
College	40 (35.7)
Cancer diagnosis	
Gynecological	101 (90.2)
Colorectal	11 (9.8)
Married or partnered (% yes)	72 (64.3)
Lives alone (% yes)	37 (33.0)
Currently employed (% yes)	19 (17.0)
Presence of metastatic disease (% yes)	88 (78.6)
Surgery prior to chemotherapy (% yes)	61 (54.5)
Symptom characteristics	Mean (SD)
Center for Epidemiologic Studies Depression Scale score	11.6 (8.2)
EORTC QLQ-C30 fatigue score	43.9 (26.3)
EORTC QLQ-C30 nausea and vomiting score	8.0 (15.2)
EORTC QLQ-C30 dyspnea score	20.5 (28.7)
EORTC QLQ-C30 insomnia score	24.7 (29.3)
EORTC QLQ-C30 appetite loss score	26.8 (34.0)
EORTC QLQ-C30 constipation score	28.9 (33.6)
EORTC QLQ-C30 diarrhea score	11.3 (23.5)
EORTC QLQ-C30 pain score	33.3 (29.8)
Physical and cognitive function measures	Mean (SD)
Gait speed (meters per second)	0.94 (0.26)
Chair stand (seconds)	13.4 (5.5)
EORTC QLQ-C30 physical function score	69.2 (21.5)
EORTC QLQ-C30 role function score	60.7 (31.5)

Abbreviations: EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; SD, standard deviation

Table(s)

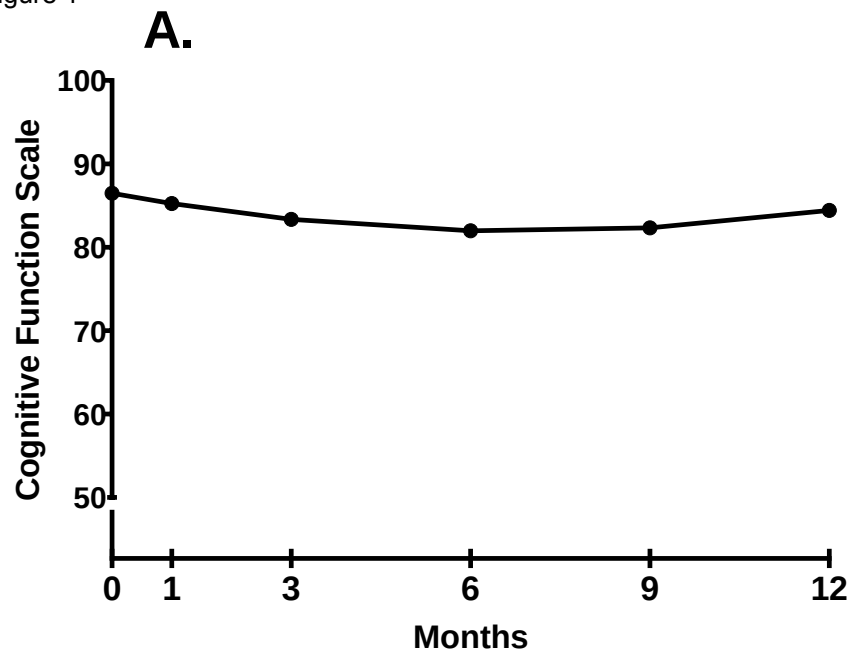
Table 2 – Hierarchical Linear Model for EORTC QLQ-C30 Cognitive Function Scale and Attentional Function Index

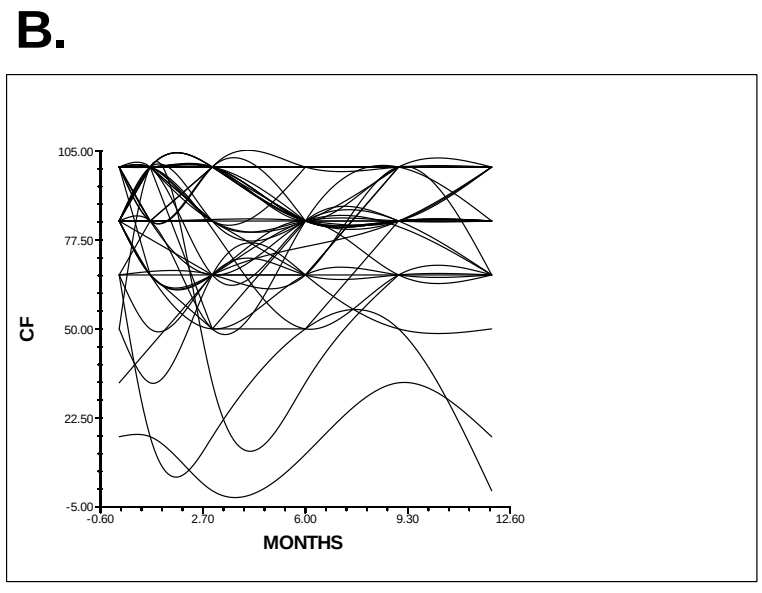
EORTC QLQ-C30 cognitive function scale	Coefficient (SE)	
	Unconditional model	Final model
Fixed effects		
Intercept	86.542 (1.606)[c]	86.479 (1.349)[c]
Time (months) (linear rate of change)	-1.314 (.446)[b]	-1.331 (.443)[b]
Time^2 (months) (quadratic rate of change)	.095 (.037)[a]	.097 (.037)[a]
Time invariant covariates		
Intercept		
Time since diagnosis		-.817 (.343)[a]
Depression		-.903 (.160)[c]
Linear		
Quadratic		
Variance components		
In intercept	203.507[c]	119.880[c]
In linear slope	1.765[ns]	1.589[ns]
In quadratic slope	.007[ns]	.006[ns]
Goodness-of-fit deviance (parameters estimated)	4221.496 (10)	4186.127 (12)
Model comparison (X^2)		35.36 (2)[c]
Attentional Function Index	Coefficient (SE)	
	Unconditional model	Final model
Fixed effects		
Intercept	7.331 (.131)[c]	7.322 (.110)[c]
Time invariant covariates		
Intercept		
Education		.531 (.164)[b]
Depression		-.073 (.014)[c]
Variance components		
In intercept	1.626[c]	1.072[c]
Goodness-of-fit deviance (parameters estimated)	1727.675 (3)	1688.367 (5)
Model comparison (X^2)		39.31 (2)[c]

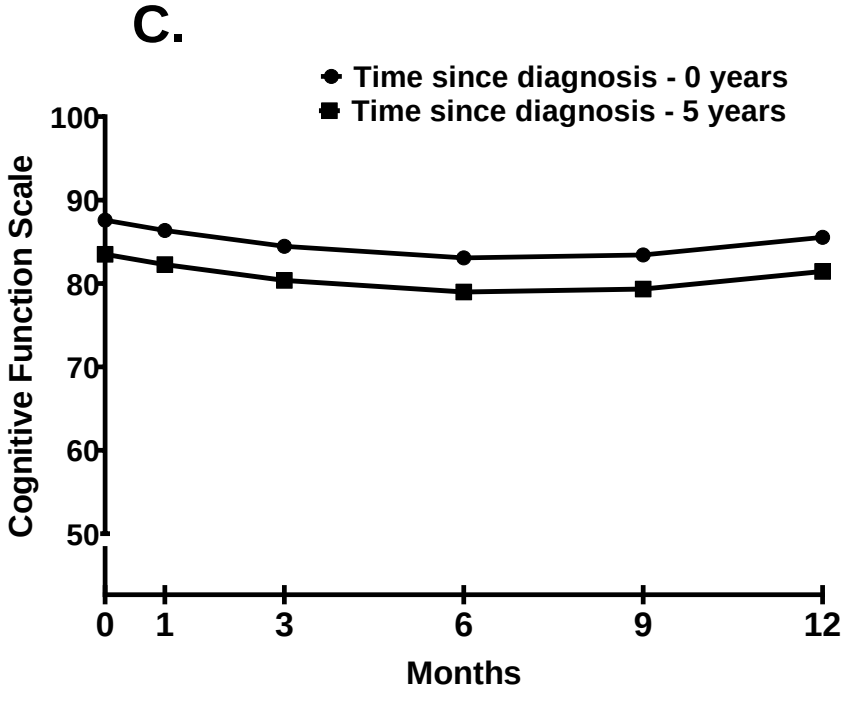
[a]p<.05, [b]p<.01, [c]p<.001

Abbreviations: EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; NS, not significant; SE, standard error

Figure 1


A.
Cognitive Function Scale
100
90
80
70
60
50
0
1
3
6
9
12
Months


B.
CF
105.00
77.50
50.00
22.50
-5.00
-0.60
2.70
6.00
9.30
12.60
MONTHS


C.
Time since diagnosis - 0 years
Time since diagnosis - 5 years
Cognitive Function Scale
100
90
80
70
60
50
0
1
3
6
9
12
Months

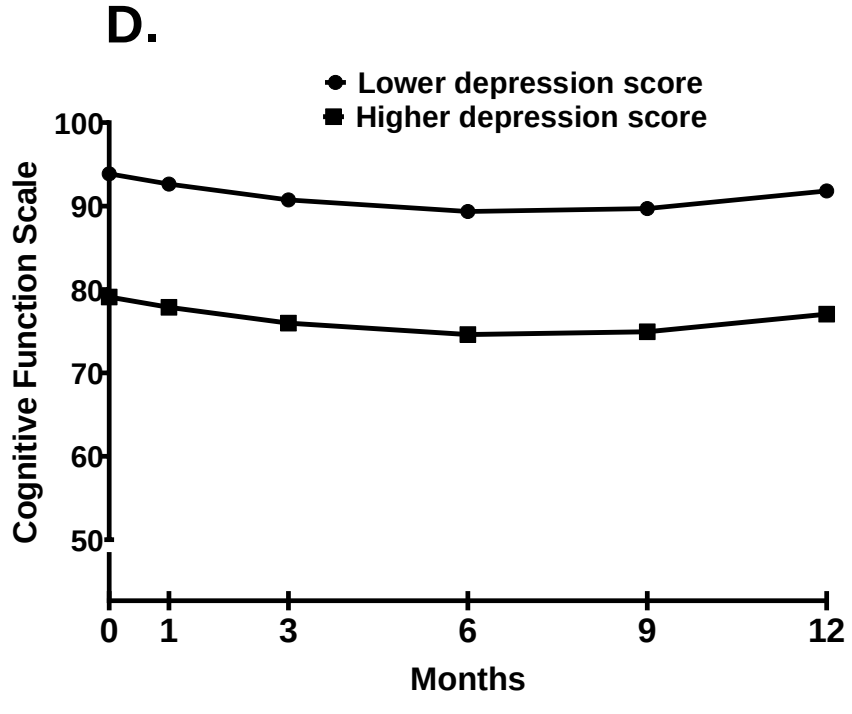
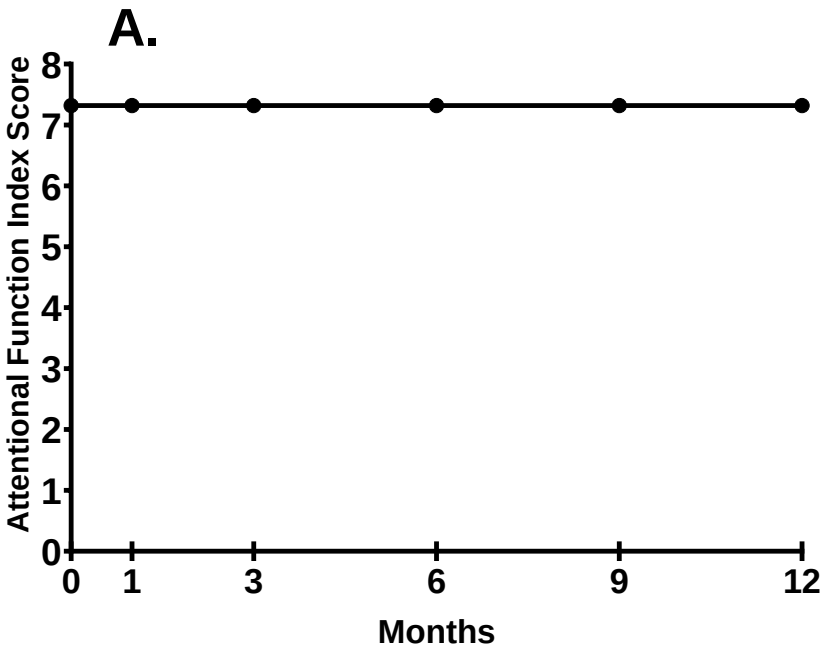
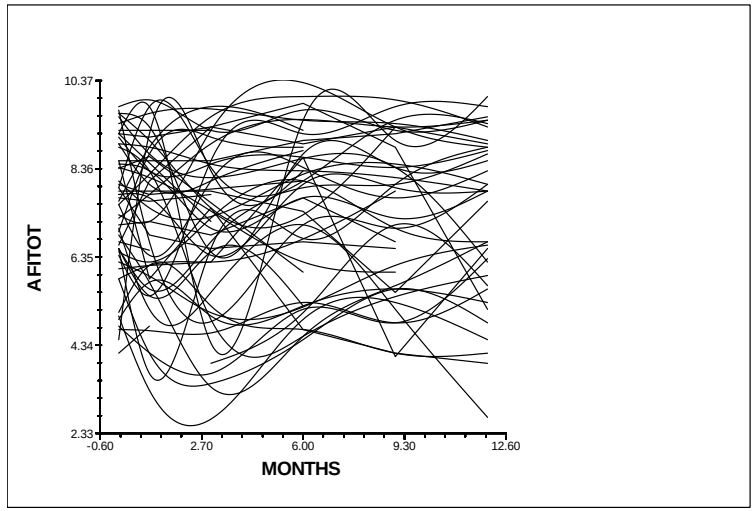
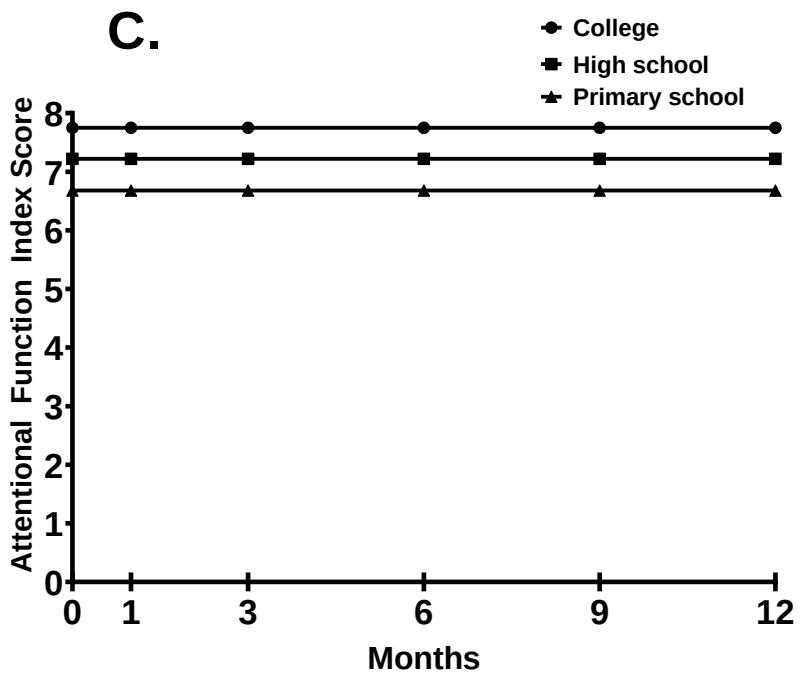
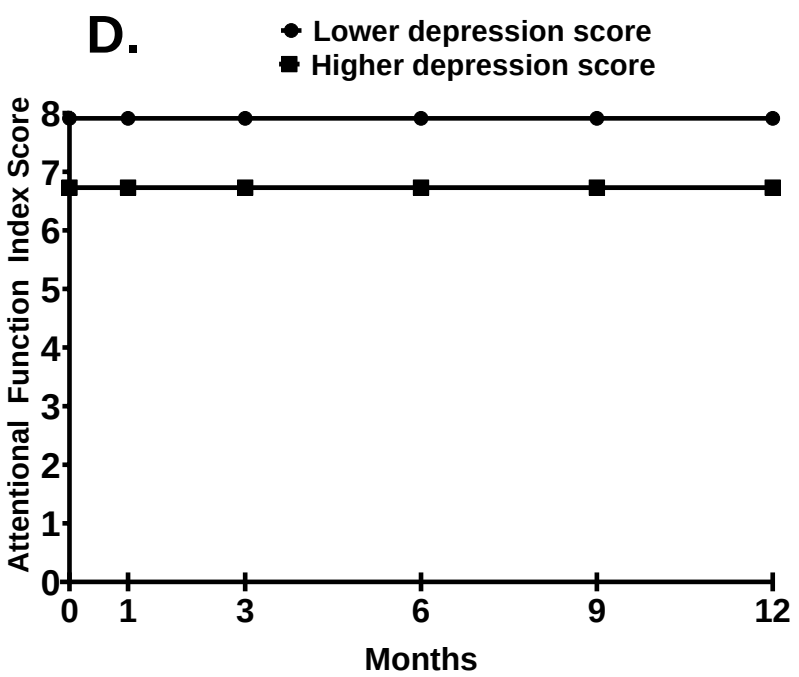

D.
Lower depression score
Higher depression score
Cognitive Function Scale
100
90
80
70
60
50
0
1
3
6
9
12
Months

Figure 2


A.
Attentional Function Index Score
0
1
2
3
4
5
6
7
8
0
1
3
6
9
12
Months


B.
AFITOT
10.37
8.36
6.35
4.34
2.33
-0.60
2.70
6.00
9.30
12.60
MONTHS


C.
College
High school
Primary school
Attentional Function Index Score
0
1
2
3
4
5
6
7
8
0
1
3
6
9
12
Months


D.
Lower depression score
Higher depression score
Attentional Function Index Score
0
1
2
3
4
5
6
7
8
0
1
3
6
9
12
Months

Supplementary Table 1 – Potential Predictors of the Intercept for the Cognitive Function Score on the EORTC-C30

Characteristics	I
Demographic characteristics	
Age in years	
Female gender	
Lives alone	
Marital status	
Currently employed	
Education	x
Clinical characteristics	
Cancer diagnosis	
Time since cancer diagnosis	x
Presence of metastatic disease	
Surgery prior to chemotherapy	
Body mass index	
Karnofsky Performance Status score	x
Number of comorbidities	
Self-administered Comorbidity Questionnaire score	x
Hemoglobin (grams/deciliter)	
Symptom severity scores	
Depression	x
Fatigue	x
Nausea and vomiting	
Insomnia	x
Appetite loss	
Constipation	
Diarrhea	
Pain	x
Dyspnea	x
Physical and cognitive function measures	
Chair stand test score (seconds)	
Gait speed (seconds)	
EORTC-C30 physical function score	x
EORTC-C30 role function score	
EORTC-C30 cognitive function score	----

Abbreviation: EORTC-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; I, Intercept

Supplementary Table 2 – Potential Predictors of the Intercept for the Attentional Function Index

Characteristics	I
Demographic characteristics	
Age in years	
Female gender	
Lives alone	
Marital status	
Currently employed	
Education	x
Clinical characteristics	
Cancer diagnosis	
Time since cancer diagnosis	
Presence of metastatic disease	
Surgery prior to chemotherapy	
Body mass index	
Karnofsky Performance Status score	x
Number of comorbidities	
Self-administered Comorbidity Questionnaire score	
Hemoglobin (grams/deciliter)	
Symptom severity scores	
Depression	x
Fatigue	x
Nausea and vomiting	
Insomnia	x
Appetite loss	
Constipation	
Diarrhea	
Pain	
Dyspnea	x
Physical and cognitive function measures	
Chair stand test score (seconds)	x
Gait speed (seconds)	
EORTC-C30 physical function score	x
EORTC-C30 role function score	
Attentional Function Index score	----

Abbreviation: EORTC-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; I, Intercept