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A prospective study of cognitive function in men with non-seminomatous germ cell tumors

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Abstract

***Objective*: Longitudinal neuropsychological assessments were performed to determine if adjuvant chemotherapy was associated with cognitive dysfunction in men with non-seminomatous germ cell tumors (NSGCT).**

***Methods*: Patients with NSGCT status post-orchiectomy that either received adjuvant chemotherapy ($n = 55$) or did not ($n = 14$) were recruited. Patients were tested before chemotherapy, 1 week post-chemotherapy (or 3 months later in the surveillance group) and 12 months after the baseline evaluation.**

***Results*: Compared with the surveillance group, patients treated with chemotherapy had higher rates of cognitive decline at 12 months (overall cognitive decline: 0%, 52%, and 67% in the surveillance, low exposure (LE), and high exposure (HE) group, respectively), greater number of tests that declined (mean of 0.1, 1.4, and 2.0 in the surveillance, LE, and HE group, respectively), and more frequent worsening in motor dexterity (0%, 48%, and 46% in the surveillance, LE, and HE group, respectively). Compared with the surveillance group, patients receiving more cycles of chemotherapy demonstrated worse psychomotor speed and learning and memory. Younger age was associated with greater incidence of overall cognitive decline at 12-month follow-up.**

***Conclusions*: Men with NSGCT that received chemotherapy demonstrated greater rates of cognitive decline in a dose-response manner. Reductions in motor dexterity were most common. Decline in learning and memory also was evident particularly at later follow-up time points and in men receiving more chemotherapy. Men that receive chemotherapy for NSGCT are at risk for cognitive decline and may benefit from monitoring and referral for psychosocial care.**

Introduction

Cognitive dysfunction in cancer patients is receiving increased attention as a survivorship issue due to its potential to interfere with occupational, scholastic, and social activities. We previously reported cognitive impairment in men with newly diagnosed non-seminomatous germ cell tumors (NSGCT) of the testis prior to receipt of chemotherapy [1]. Similar findings have been reported for patients with breast [2–5], prostate [6], and small cell lung cancers [7]. Recent preclinical studies have shed light on the neurobiologic mechanisms of neurotoxicities associated with some chemotherapies—the interested reader is referred to the following reviews [8,9].

Studies with longitudinal designs that include cognitive testing prior to chemotherapy are necessary to identify treatment-related cognitive decline [10,11]. Reports from longitudinal trials have documented treatment-related cognitive decline in 13–70% of patients with breast cancer who receive chemotherapy [12]. To date, three retrospective cross-sectional studies [13–15] and one prospective study that conducted longitudinal testing in a histologically mixed sample of testicular cancer patients [16] have been reported. Skaali *et al*. found no difference in rates of cognitive change 1 year after completion of chemotherapy between patients that received no chemotherapy, one cycle of chemotherapy, or multiple cycles of chemotherapy. However, rates of decline on individual cognitive tests ranged from 0–7% in patients who did not receive chemotherapy versus 0–23% in patients who received chemotherapy. Additionally, the development of tinnitus (a well-known neurotoxicity of platinum-based chemotherapies) was 3.5 times more frequent (21% vs. 6%) in patients with cognitive decline versus those without cognitive decline.

Given the excellent long-term survival of many testicular cancer patients, it is of critical importance to understand the nature, extent, and temporal course of disease-related symptoms and treatment-related toxicities to help direct survivorship research and clinical care [17].

Methods

Study site and participants

Newly diagnosed patients with NSGCT from the genitourinary medical service of MD Anderson Cancer Center, Houston, Texas were recruited. Details about eligibility requirements and recruitment have been previously published [1]. Upon enrollment, the research staff obtained informed consent from all participants.

Procedures

A systematic, consecutive sampling procedure was used to identify participants. Patients with newly diagnosed NSGCT were identified from clinic schedules. Research staff reviewed medical records to evaluate the eligibility criteria. Eligible patients were recruited to the study after orchiectomy but prior to receiving adjuvant treatment. Two groups of patients were recruited, a surveillance group that did not receive adjuvant therapy and a group that received adjuvant chemotherapy. The chemotherapy group was further separated into a low exposure (LE) (2–3 cycles of chemotherapy) and a high exposure (HE) group (4–7 cycles of chemotherapy). At the time of study enrollment, participants completed a baseline assessment consisting of cognitive tests and self-report measures. A 'post-treatment' assessment was completed 1 week after adjuvant chemotherapy or 3 months after the baseline assessment for participants who did not receive chemotherapy. The final assessment was completed 12 months after baseline. Each assessment required 60 minutes. The study was approved by the institutional review board of MD Anderson Cancer Center.

Measures

A battery of six neuropsychological tests assessing multiple cognitive domains including attention, psychomotor speed, learning and memory, language, executive, and motor function was administered (Wefel *et al.* [1]). Published normative data that adjust for age, education, handedness, and gender where appropriate were used to convert raw test scores to standardized scores (z-scores; mean = 0, SD = 1) to facilitate comparisons among measures. Alternate forms were used when available to minimize practice effects.

The self-report assessment consisted of sociodemographic and psychosocial measures. Depressive symptoms were assessed with the Centers for Epidemiologic Studies-Depression (CES-D) scale [18], and anxiety was assessed using the State-Trait Anxiety Inventory (STAIS) [19]. Clinically significant symptoms of distress (i.e., depressive or anxious symptoms) were defined as ratings on the CES-D $\geq$ 27 (raw score) and STAIS $<$ 5th percentile. Evidence from medically ill populations suggests that the cut-off score of 27 on the CES-D provides better sensitivity and specificity compared with other commonly used cut offs [20,21].

Disease stage and tumor marker (i.e., alpha fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase) data were collected from the medical records. Staging was determined using the American Joint Committee on Cancer Staging for Testicular Germ Cell Tumors criteria [22], and risk categories were determined as defined by the International Germ Cell Cancer Collaborative Group [23].

Statistical analysis

Change in cognitive function was determined using the standardized regression-based (SRB) approach used by Stewart *et al.*[24] and proposed by Mcsweeny *et al.* [25] and Sawrie *et al.* [26] SRB regression models were developed using the standardized scores for each cognitive test. Age and education were included as covariates in all regression models given their well-known relationship with cognitive function. Using the surveillance group, the 3-month post-treatment follow-up time point was regressed on the baseline time point for the first model (post-treatment model), and the 12-month follow-up time was regressed on the 3-month post-treatment follow-up for the second model (12-month model). An SRB score at the 3-month post-treatment time point was generated for each subject by subtracting the actual score from the post-treatment model predicted score and then dividing by the standard error of the estimate derived from the surveillance group. The SRB score at the 12-month time point was similarly generated using the 12-month model. This score is expressed in standard deviation units and reflects either improvement or decline in cognitive function. Cognitive decline on a specific test was defined as an SRB score of < -2.0. Cognitive improvement on a specific test was defined as an SRB score of $> +2.0$. Overall cognitive decline was defined as declining on >2 tests, and overall cognitive improvement was defined as improving on >2 tests.

Standardized regression-based change scores were computed, and percent declined or improved on each test was compared between treatment groups. To test for treatment group differences, Chi-square and Fisher's exact test were used to identify differences in the percentages of people declining on each neurocognitive test and in the incidence of overall cognitive decline at the post-treatment and 12-month follow-up time points. Analysis of variance (ANOVA) and Kruskal–Wallis tests were utilized to test if

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Table 1. Baseline differences in demographic and clinical factors, and cognitive test results by treatment group

Domain	Test	S ($n=14$)	LE ($n=25$)	HE ($n=30$)	p-value
Mean (SD)					
Attention	DSpan[a]	−0.2 (0.6)	−0.1 (0.8)	0.03 (1.0)	0.672
Psychomotor Speed	DSymbol[a]	0.4 (0.6)	0.3 (1.0)	0.3 (1.0)	0.944
	TMTA[a]	0.7 (0.6)	0.3 (0.7)	0.1 (1.3)	0.787
Learning and Memory	HVLT[a]	−0.4 (0.9)	−1.2 (1.5)	−1.1 (1.2)	0.561
Executive	TMTB[a]	−0.2 (2.5)	−0.4 (1.8)	−0.8 (2.1)	0.427
Language	COWA[a]	0.5 (0.9)	0.2 (0.9)	0.2 (1.0)	0.684
Motor	GPD[a]	−0.2 (0.8)	−0.9 (1.0)	−1.1 (1.7)	0.135
	GPND[a]	−0.5 (0.9)	−0.6 (0.9)	−0.7 (1.1)	0.429
Age (years)		34.4 (5.7)	32.4 (7.4)	28.4 (7.5)	0.065
Education (years)		15.4 (1.9)	14.5 (3.1)	14.3 (2.6)	0.385
Depression	CESD[b]	10.2 (9.7)	15.6 (11.5)	12.1 (10.3)	0.470
Anxiety	STAIS[a]	0.6 (1.0)	−0.3 (1.2)	0.1 (1.2)	0.103
% (N)					
Stage of disease					
Stage 1		92.9 (13)	76.0(19)	60.0 (18)	0.174
Stage 2		7.1 (1)	16.0(4)	16.7 (5)	
Stage 3		0 (0)	8.0(2)	23.3 (7)	

S, surveillance; LE, low exposure chemotherapy; HE, high exposure chemotherapy; DSpan, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span [30]; DSymbol, WAIS-R Digit Symbol [30]; TMTA, Trail Making Test A [31]; HVLT, Hopkins Verbal Learning Test [32]; TMTB, Trail Making Test B [31]; COWA, Controlled Oral Word Association [33]; GPD/ND, Lafayette Grooved Pegboard dominant/non-dominant hand [34]; CES-D, Center for Epidemiological Studies-Depression [18], STAIS, State-Trait Anxiety Inventory-State [19].
[a]Z-score.
[b]Raw score.

the number of tests showing decline was different between groups. Fisher's exact test and independent sample tests were used to identify predictors of decline/improvement. Unadjusted results are presented because of the exploratory nature of this study. Results were summarized using frequencies, percentages, means, standard deviations, and p-values. All analyses were conducted using SAS version 9.1 and SPSS 12.0.

Results

Sixty-nine patients with NSGCT completed neuropsychological evaluation (Table 1). Mean age was 31.0 (±7.5) years (range 18.5–50.7 years). On average, patients had completed 14.6 years (±2.7) of education (range 8–20 years). Ethnically, 52 (75%) were Caucasian, 12 (17%) were Hispanic, 3 (4%) were African American, and 2 (2%) were of other ethnicities.

Low exposure chemotherapy patients ($n=25$) received the following regimens: CEB × 2 ($n=4$), CEB × 3 ($n=1$), BEP × 2 ($n=9$), BEP × 3 ($n=10$), and BEP × 2 and ATP × 1 ($n=1$). High exposure chemotherapy patients ($n=30$) received the following regimens: CEB × 4 ($n=3$), BEP × 4 ($n=11$), EP × 4 ($n=1$), BEP × 2 and EP × 2 ($n=2$); and one patient received each of the following regimens: CISCA/VB × 4, CISCA/VB × 1 and ACE × 3, CISCA/VB × 5, CISCA/VB × 6, CISCA/VB × 2 and ACE × 2 and BEP × 2, CISCA/VB × 2 and ACE × 3 and BOP × 1 and POMB × 1, BEP × 4 and ATP × 2, BEP × 4 and VIP × 2, and, BEP × 3 and CISCA × 2 and EP × 1. The median and Fisher's exact tests showed no significant differences between groups at baseline on age, education, stage of disease, depression, anxiety, or any of the neurocognitive tests (Table 1). Mean group performances at the post-treatment and 12-month follow up time point are presented in Tables 2 and 3.

Sixty-two patients completed the post-treatment assessment, and 54 patients completed the 12-month assessment. Attrition was highest in the surveillance group, 21.4% at the post-treatment follow-up, and 35.7% at the 12-month follow-up. Attrition in the LE group was 8% and 16% at the post-treatment and 12-month follow-up

Table 2. Mean cognitive test performances by treatment group at the post-treatment time point

Domain	Test[a]	S ($n=11$)	LE ($n=23$)	HE ($n=28$)
Mean (SD)				
Attention	DSpan	0.2 (1.2)	0.04 (0.8)	0.2 (1.0)
Psychomotor speed	DSymbol	0.5 (0.6)	0.7 (0.9)	0.3 (1.1)
	TMTA	0.6 (0.7)	0.5 (0.5)	0.1 (1.3)
Learning and Memory	HVLT	−1.0 (1.0)	−1.0 (1.2)	−1.0 (1.2)
Executive	TMTB	0.03 (1.4)	−0.02 (1.2)	−0.3 (2.2)
Language	COWA	0.4 (1.1)	0.1 (0.8)	0.4 (1.1)
Motor	GPD	0.1 (0.9)	−1.3 (1.3)	−1.0 (1.9)
	GPND	−0.1 (0.5)	−0.8 (1.5)	−0.6 (0.9)

S, surveillance; LE, low exposure chemotherapy; HE, high exposure chemotherapy; DSpan, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span [24], DSymbol, WAIS-R Digit Symbol [24] , TMTA, Trail Making Test A [25]; HVLT, Hopkins Verbal Learning Test [26]; TMTB, Trail Making Test B [25]; COWA, Controlled Oral Word Association [27]; GPD/ND, Lafayette Grooved Pegboard dominant/non-dominant hand [28].
[a]Z-score.

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Table 3. Mean cognitive test performances by treatment group at the 12-month time point

Domain	Test[a]	S ($n=9$)	LE ($n=21$)	HE ($n=24$)
Mean (SD)				
Attention	DSpan	0.1 (1.1)	0.05 (0.9)	0.2 (1.1)
Psychomotor speed	DSymbol	0.6 (0.8)	0.9 (0.8)	0.5 (1.0)
	TMTA	0.9 (0.4)	0.7 (0.7)	0.4 (1.1)
Learning and Memory	HVLT	−0.5 (0.4)	−0.6 (0.7)	−0.9 (1.3)
Executive	TMTB	0.6 (0.6)	0.3 (1.3)	−0.2 (1.4)
Language	COWA	0.6 (1.0)	0.1 (1.1)	0.4 (1.3)
Motor	GPD	0.2 (0.6)	−0.4 (1.2)	−0.7 (2.1)
	GPND	0.3 (0.6)	−0.5 (1.1)	−0.3 (0.7)

S, surveillance; LE, low exposure chemotherapy; HE, high exposure chemotherapy. DSpan, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span [24]; DSymbol, WAIS-R Digit Symbol [24]; TMTA, Trail Making Test A [25]; HVLT, Hopkins Verbal Learning Test [26]; TMTB, Trail Making Test B [25]; COWA, Controlled Oral Word Association [27]; GPD/ND, Lafayette Grooved Pegboard dominant/non-dominant hand [28].
[a]Z-score.

assessments, respectively. The HE group's attrition rates were 6.7% and 20% at the post-treatment and 12-month follow-up assessments, respectively. Baseline comparisons between completers and dropouts at the post-treatment and 12-month follow-up showed no differences in cognitive test performance, age, education, stage of disease, CES-D, or STAIS.

SRB change scores over time—baseline to post-treatment follow-up

Both LE and HE groups (versus surveillance group) demonstrated greater rates of decline in dominant hand fine motor dexterity (Table 4). The HE group additionally evidenced greater decline on a measure of psychomotor speed. There were no statistically significant differences in the frequency of overall cognitive decline, although there was a trend suggesting greater impairment that appeared to be related to the extent of exposure to treatment, with 0% showing overall cognitive decline in the surveillance group, 17% in the LE group, and 29% in the HE group. Using ANOVA, both the LE and HE groups declined on significantly more tests than the surveillance group (Table 4, Figure 1). These results were verified with the non-parametric Kruskal–Wallis test.

There were no between group differences in overall cognitive improvement. Compared with the surveillance group, the LE group demonstrated more frequent improvement on a measure of psychomotor speed (DSymbol: surveillance = 0%, LE = 39%, HE = 7%; $p < 0.05$). There were no other statistically significant differences on any individual cognitive test. However, the HE group improved on significantly more tests than the surveillance group (Kruskal Wallis $p < 0.05$).

Standardized regression-based change scores over time—post-treatment to 12-month follow-up

Both LE and HE groups demonstrated greater rates of decline (versus surveillance group) in dominant hand fine motor dexterity (Table 5). The HE group additionally evidenced greater decline on a measure of psychomotor speed. Learning and memory showed a trend toward greater decline in the HE group. LE and HE groups evidenced significantly greater rates of overall cognitive decline and declined on more tests compared with the surveillance group (Table 5, Figure 2).

The LE and HE groups did not demonstrate a statistically significant difference (versus surveillance group) in rates of

Table 4. Cognitive decline from baseline to post-treatment by treatment group

Domain	Test	S ($n=11$)	LE ($n=23$)	HE ($n=28$)	Fisher's exact p (LE versus S)	Fisher's exact p (HE versus S)
Percent declined						
Attention	DSpan	0	0	0	*	*
Psychomotor Speed	DSymbol	0	9	39	1.0	0.017
	TMTA	0	4	14	1.0	0.309
Learning and Memory	HVLT	0	4	0	1.0	*
Executive	TMTB	9	4	7	1.0	1.0
Language	COWA	0	0	0	*	*
Motor	GPD	0	35	39	0.034	0.017
	GPND	0	22	14	0.150	0.309
Overall Decline[a]		0	17	29	0.280	0.08
Mean (SD)						
Number tests declined (ANOVA)		0.1 (0.3)	0.8 (0.9)	1.1 (1.0)	0.05	0.005

S, Surveillance; LE, low exposure chemotherapy; HE, high exposure chemotherapy; DSpan, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span; DSymbol, WAIS-R Digit Symbol; TMTA, Trail Making Test A; HVLT, Hopkins Verbal Learning Test; TMTB, Trail Making Test B; COWA, Controlled Oral Word Association, GPD/ND, Lafayette Grooved Pegboard dominant/non-dominant hand.
[a]Decline on >2 tests.
*No statistics computed because of zero declines in both groups.

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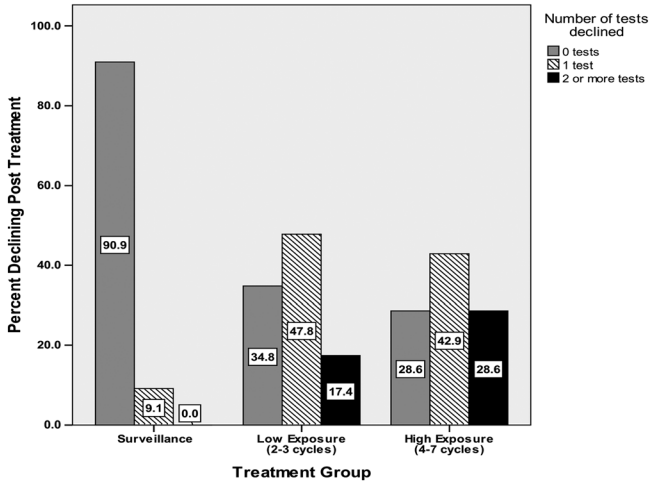

Figure 1. Cognitive decline from baseline to post-treatment on 0, 1, and 2+ tests by group

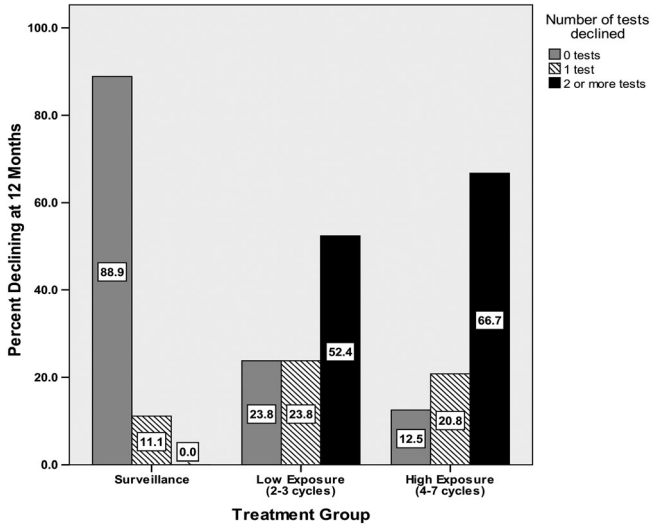

Figure 2. Cognitive decline from post-treatment to 12 months on 0, 1, and 2+ tests by group

improvement on any test or in overall improvement. However, parametric and non-parametric analyses demonstrated that both the LE and HE groups improved on significantly more tests than the surveillance group (ANOVA $p < 0.05$, Kruskall Wallis $p < 0.05$).

Predictors of cognitive change at the post-treatment and 12-month follow-up

Bivariate exploratory analyses using Fisher's Exact tests and independent sample tests were used to examine if the following covariates exhibited potential association with overall cognitive decline or improvement at the post-treatment and 12-month time points: biomarkers (alpha fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase), age, depression, state anxiety, years of education, risk status based on the International Germ Cell Cancer Collaborative Group, baseline cognitive impairment, and stage of disease. Overall decline post-treatment was not associated with any of these predictors. At the 12-month follow-up, only age was related to overall decline, with those who declined being younger (mean age = 28.1 years; SD = 7.5) compared with non-decliners (mean age = 33.6; SD = 6.8). There was no relationship between any of the predictors and overall cognitive improvement at the post-treatment or 12-month follow-up.

Table 5. Cognitive decline from post-treatment to 12-month follow-up by treatment group

Domain	Test	S ($n = 9$)	LE ($n = 21$)	HE ($n = 24$)	Fisher's exact p (LE versus S)	Fisher's exact p (HE versus S)
Percent declined						
Attention	DSpan	0	10	0	1.0	*
Psychomotor speed	DSymbol	0	0	0	*	*
	TMTA	0	19	58	0.287	<0.005
Learning and Memory	HVLT	0	14	33	0.534	0.073
Executive	TMTB	0	14	21	0.534	0.290
Language	COWA	11	24	13	0.637	1.0
Motor	GPD	0	10	25	1.0	0.156
	GPND	0	48	46	0.013	0.015
Overall decline[a]		0	52	67	0.006	0.001
Mean (SD)						
Number tests declined (ANOVA)		0.1 (0.3)	1.4 (1.0)	2.0 (1.2)	0.001	<0.0001

S, surveillance; LE, low exposure chemotherapy; HE, high exposure chemotherapy; DSpan, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span; DSymbol, WAIS-R Digit Symbol; TMTA, Trail Making Test A; HVLT, Hopkins Verbal Learning Test; TMTB, Trail Making Test B; COWA, Controlled Oral Word Association; GPD/ND, Lafayette Grooved Pegboard dominant/non-dominant hand.

[a]Decline on >2 tests.

*No statistics computed because of zero declines in both groups.

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Discussion

Men with NSGCT who received chemotherapy evidenced more frequent overall cognitive decline and decrease in psychomotor speed. They also evidenced decline on a greater number of tests at both the post-treatment and 12-month follow-up time points when compared with men with NSGCT who did not receive chemotherapy. Additionally, decline in learning and memory at the 12-month follow-up was more common in men who received more cycles of chemotherapy. At both time points, there appeared to be a 'dose-response' relationship suggesting that greater chemotherapy exposure was associated with decline on more tests and greater overall cognitive decline. However, it is not possible to distinguish if the impact on cognition was due to the dose versus the regimen of chemotherapy given.

Our exploratory analysis indicated that younger age was potentially associated with a greater incidence of overall cognitive decline at the 12-month follow-up. However, after controlling for chemotherapy group due to trends toward statistically significant differences in mean age between groups, this effect was no longer significant. There was no association between stage of disease, risk status, clinical biomarkers, baseline cognitive impairment, education, or changes in mood and the development of cognitive decline or improvement at any time point. It is possible that younger patients were more at risk for androgen suppression and the associated adverse effects on cognition [27]. Unfortunately, testosterone levels were not serially monitored in the current study. It is also possible that this finding is an artifact of age being confounded with treatment exposure.

At the post-treatment time point, men treated with chemotherapy were more likely to demonstrate improvements in psychomotor speed. Similarly, men treated with chemotherapy demonstrated improvement on a greater number of tests at the 12-month follow-up time point. Although there were no mean group differences on cognitive tests at baseline, more men treated with chemotherapy were performing at lower levels on six out of eight tests, which may have resulted in greater rates of regression to the mean and the appearance of more frequent improvement. Improvement may also reflect beneficial effects of treatment on unexamined disease factors. Importantly, there were not between group differences in distributions of patients performing at the upper limits of the tests that would confound interpretation of differential rates of decline.

Many of the patients received chemotherapy regimens with platinum-containing agents, which are known to be associated with peripheral neuropathy. It is therefore not surprising that they exhibited declines in upper extremity fine motor dexterity and tests of psychomotor function. Surprisingly, Skaali *et al.* [16] did not report adverse effects on motor function in their patients who were also treated with platinum-containing regimens.

Using a similar battery of tests that assessed similar cognitive domains, Skaali *et al.*[16] reported cognitive decline in approximately 15% of patients treated with chemotherapy. In our study, cognitive decline post-treatment was identified in 17% and 29% in the LE and HE exposure groups, respectively. At 12 months, cognitive decline was identified in 52% and 67% of the LE and HE exposure groups, respectively. The difference in rates of cognitive impairment between the current study and that of Skaali *et al.* is quite substantial, particularly at the 12-month follow-up. This may be due in part to our sample being more heavily treated; however, even our LE chemotherapy group experienced much higher rates of cognitive decline.

The observation of increased rates of cognitive decline at the 12-month follow-up when patients were off treatment calls attention to potential late effects [11] and the survivorship issues these cancer patients must face [17]. Additional longitudinal studies with long-term post-treatment follow-up assessments appear warranted to examine the course of cognitive decline after completion of chemotherapy.

There was an evidence of adverse impact on learning and memory; however, this appears to have occurred less frequently than we have seen in women with breast cancer [11]. In the present study, we employed an SRB approach to define cognitive change, as it has been previously demonstrated to identify cognitive decline more frequently compared with a reliable change index (RCI) approach and can simultaneously control for the impact of covariates [28]. However, the surveillance sample used to generate the regression equations was small and may not be representative of the larger NSGCT population that does not receive chemotherapy. When we analyzed our data using the practice effect adjusted RCI methodology (RCI + PE, data not shown), as we have previously performed in studies of chemotherapy in breast cancer survivors [11], there were no statistically significant between group effects on any test, lower rates of treatment associated decline in memory function (18%, 4%, and 11%, respectively, for the surveillance, LE, and HE groups) than that observed with the SRB methodology, similar rates of overall decline post-treatment (9%, 22%, and 29%, respectively, for the surveillance, LE, and HE groups), and lower rates of cognitive decline at the 12-month follow-up time point (0%, 14%, and 8%, respectively, for the surveillance, LE, and HE groups). However, we must caution about making direct comparisons between the SRB results in men with NSGCT and the RCI + PE results in women with breast cancer. As demonstrated by Ouimet *et al.* [28], these approaches can yield different results because of the fact that SRB methodology allows for inclusion of covariates and predicts change scores using the same test–retest interval for all groups. When considering the RCI + PE analyses, compared with our previous studies demonstrating chemotherapy-related cognitive dysfunction in women with breast cancer that received

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largely 5-fluorouracil, doxorubicin, cyclophosphamide-based chemotherapies, it appears that men with NSGCT who receive platinum-containing regimens have less frequent decline in memory, which deserves further attention and may reflect differential effects of chemotherapy regimens and differences in other aspects of the patient populations (e.g., age).

Although our consent rate was good (76%) in this relatively rare tumor type, the small sample sizes in each group, high attrition especially in the surveillance group and heterogeneous chemotherapy regimens in the LE and HE groups, are limitations that may impact the power of the analyses. Additionally, the current sample derived from a large tertiary cancer center may not be representative of all NSGCT patients.

We previously reported an unexpectedly high incidence of pretreatment cognitive dysfunction in men with NSGCT [1]. The results of the current study further demonstrate that men who receive chemotherapy experience greater declines in motor function that is likely consistent with the development of peripheral neuropathy in individuals treated with platinum-containing agents. Additionally, greater exposure to chemotherapy was associated with stronger effects on overall cognitive decline and the number of tests showing decline at post-treatment and the 12-month follow-up as well as more frequent decline in learning and memory at the 12-month follow-up. The observation of a 'dose-response' relationship between chemotherapy exposure and cognitive dysfunction has been previously reported in women with breast cancer [29] and suggests that NSGCT patients with greater chemotherapy exposure are at increased risk for adverse cognitive outcomes and may benefit from closer monitoring. However, we are not able to rule out an alternative explanation that the regimens used in the HE group, and not the 'dose', are the primary cause of cognitive decline. Although there was no evidence that any demographic, clinical, mood, or biomarker variable was associated with cognitive dysfunction immediately after chemotherapy, younger age was associated with cognitive decline at the long-term follow-up time point. Replication of this finding is necessary in order to establish if this is a reliable predictor of an at-risk subgroup that may benefit from closer monitoring or risk adapted therapy. Because of the absence of longitudinal data on hormonal function, we were unable to determine if alterations in men's hormonal milieu contribute to cognitive dysfunction.

Given the epidemiology of NSGCT, most men are young at the time of diagnosis, in the midst of their careers and with numerous social demands that require optimal cognitive functioning. Identifying affected patients is important so that psychosocial support and compensatory interventions may be offered to patients experiencing these symptoms

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