Heterogeneous Response of Chemotherapy-Related Cognitive Decline in Patients with Breast Cancer: A Prospective Study

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Abstract

Objective: A significant proportion of adjuvant-treated breast cancer patients experience cognitive decline, challenging the person's ability to return to normal activities after treatment. However, not every patient experiences cognitive problems, and even in patients with impairments, determining clinically important cognitive decline remains challenging. Our objective was to explore differences in neuropsychological performance following adjuvant chemotherapy (CT) in patients with breast cancer. **Method**: We conducted a prospective observational study in an Oncology Breast Clinic and assessed neuropsychological performance before and after adjuvant CT and in non-CT-treated women with breast cancer and healthy controls (HCs). Standardised between-group differences and regression-based change scores were calculated. **Results**: CT-treated patients ($n = 66$) performed significantly different from non-CT-treated patients ($n = 39$) and HCs ($n = 56$). There was a significant effect on verbal fluency ($p = .0013$). CT performed significantly worse than non-CT and HC [effect size (ES) = .89, $p < .001$ and ES = .61, $p \leq .001$, respectively] and from HCs with regard to proactive interference (ES = .62, $p \leq .001$). Regression-based scores revealed more severe cognitive decline in the CT-treated group [24.24% (16/66)] than in the non-CT-treated group [15.20% (6/39)] and HC group [7.14% (4/56)]. Patients who underwent CT and showed cognitive decline were less educated and older, with significantly lower baseline scores. **Conclusions**: CT-treated patients showed more vulnerability on cognitive control and monitoring than non-CT-treated breast cancer patients and HCs. Older patients with less education and lower baseline cognitive performance represent a group at risk for cognitive decline following CT. Identification of patients at risk for decline could improve targeted support and rehabilitation.

Keywords: Breast cancer, Chemotherapy, Cognitive dysfunction, Neuropsychology, Executive function, Memory

INTRODUCTION

Breast cancer is the most common cancer in women worldwide with 201 million newly diagnosed cases in 2018 (Bray et al., 2018). Improved treatment results in an approximately 90% disease-free 5-year survival rate, with a sustained rise in long-term survival rates (Noone et al., 2018). However, patients are often left with a cluster of symptoms that negatively affect their quality of life (Mitchell, 2007; Mols, Vingerhoets, Coebergh, & van de Poll-Franse, 2005), thereby influencing their abilities to regain everyday function and resume vocational and social activities (De Vries, Den Oudsten, Jacobs, & Roukema, 2014).

Recently, the gradual shift towards patient-reported outcomes has led to the examination of the impact of cancer and its treatment on cognitive function, one of the most common concerns raised by breast cancer survivors, and an aspect of everyday function that is critical to normal performance. The term 'chemobrain' expresses the burden experienced by long-term survivors (Schagen et al., 2014).

A considerable number of neuropsychological studies, supported by animal models and neuroimaging research, suggest cognitive changes in breast cancer survivors, especially following chemotherapy (CT) (Pomykala, de Ruiter, Deprez, McDonald, & Silverman, 2013; Seigers, Schagen, Van Tellingen, & Dietrich, 2013). Although CT is known to be

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cytotoxic to the central nervous system (CNS), prior research showed that 'chemobrain' is a complex phenomenon involving various factors. Besides chemo-induced toxicity, hormonal changes and inflammatory processes are likely to contribute to the development of cognitive problems (Ahles & Saykin, 2007; Nelson & Suls, 2013; Scherling et al., 2011; Wefel & Schagen, 2012). Also, psychological distress and fatigue could theoretically result in impaired neuroplasticity and impaired cognitive performance (Andreotti, Root, Ahles, McEwen, & Compas, 2015; Hermelink, 2015). Various candidate mechanisms and a spectrum of symptoms should be considered when cancer-associated cognitive decline is investigated (Ahles & Saykin, 2007; Ahles & Hurria, 2018; Andreotti et al., 2015; Hermelink, 2015; Wefel & Schagen, 2012).

Cognitive domains most commonly affected in breast cancer patients are attention and processing speed, memory, and executive function. The latter includes working memory, cognitive flexibility, and multitasking (Ahles et al., 2010; Wefel, Saleeba, Buzdar, & Meyers, 2010). Root, Andreotti, Tsu, Ellmore, and Ahles (2016) argued that memory is not affected per se, but that an inefficiency in learning is wrongly perceived by patients as forgetting, possibly due to inefficiency of attentional processes. Chen, Xu, Li, Tang, and Wang (2016) showed that following CT, patients had selective abnormality in alerting and executive control networks. These findings should be considered when selecting the cognitive domains to measure in neuropsychological assessment.

There are two major challenges in translating clinically observed symptoms to standardised measures of cognitive impairment. Firstly, various methods are used to define cognitive decline after cancer at the individual level. Most studies define impairment as a clinically relevant difference when comparing patient performance to normative data or performances of non-CT-treated patients or healthy controls (HCs). The boundary between normal and impaired function depends upon arbitrary thresholds, as it relates to both patient performance and the normative standard to which it is compared (Schilder et al., 2010; Shilling, Jenkins, & Trapala, 2006). Therefore, it may be interesting to focus on patient performance before therapy, rather than a normative score, since even in affected patients, post-treatment scores usually stay within normal boundaries (Jenkins et al., 2006). Moreover, the degree and nature of cognitive impairment after cancer are usually assessed in terms of statistical differences in neuropsychological performance between treatment groups. By estimating differences in performance, a statistical threshold of significance relates to clinical differences and sample characteristics, such as group size. Therefore, by comparing performance between groups, statistical significance should be accompanied by a normalisation of scores that are typically observed in the population to provide information on the severity and impact of cognitive burden (Bernstein, McCreath, Komeylian, & Rich, 2017; Menning et al., 2016).

Secondly, not all patients following the same treatment trajectory experience cognitive decline to the same extent, or even at all. Some patients might even show cognitive 'improvement', a common finding after repeated assessments, known as the test–retest effect. Accordingly, average group scores may appear stable over time, while individual cases may show marked differences. Thus, even if no mean difference between treatment groups can be found, it remains important to examine the possibility of a vulnerable sub-population of 'at-risk' patients (Schagen, Muller, Boogerd, Mellenbergh, & van Dam, 2006), which requires further exploration of individual risk factors to optimise rehabilitation programs.

Our goal was to investigate the prevalence of declined performance on neuropsychological tests grouped into the domains of executive function, verbal memory, and processing speed before and immediately after CT for breast cancer, compared to performance in non-CT-treated patients and HCs. We focused on the effect sizes (ESs) of between-group differences in performance change between baseline and post-treatment measurements and considered the possibility of a vulnerable sub-population with a regression-based model to identify patients with significant cognitive decline.

METHOD

Participants

Patients were recruited at Ghent University Hospital Breast Clinic between August 2010 and December 2012. All patients were between 25 and 65 years of age with newly diagnosed carcinoma of the breast. They were selected for adjuvant treatment after surgery. One patient group received CT [5-fluorouracil, epirubicin, and cyclophosphamide (FEC)] every 21 days for three cycles, followed by three cycles of docetaxel (D) CT (CT group), and, if necessary, radiotherapy (RT) and/or endocrine therapy (ET). The other patient group received RT and/or ET only (non-CT group). The HC group was recruited from age-matched family and friends of participants, and women who responded to the invitation to participate on the website of the hospital. Eligibility screening excluded women with any history of cancer diagnoses and treatment, and with psychiatric or neurological disorders, as well as those not fluent in Dutch. Potential eligible patients were approached by their healthcare providers. The first author provided information and obtained informed consent. Of the 196 patients eligible, 111 agreed to participate. The main reason for refusal was that participation was considered too burdensome. One patient was excluded because of an inability to comprehend task instructions (Figure 1).

All participants provided written informed consent. The Ethical Committee of Ghent University Hospital approved the protocol (ref: B67020108507).

Procedure

After surgery, but before the start of adjuvant treatment (T1), each participant completed a standardised neuropsychological battery of approximately 1 hour in a set order. For the CT
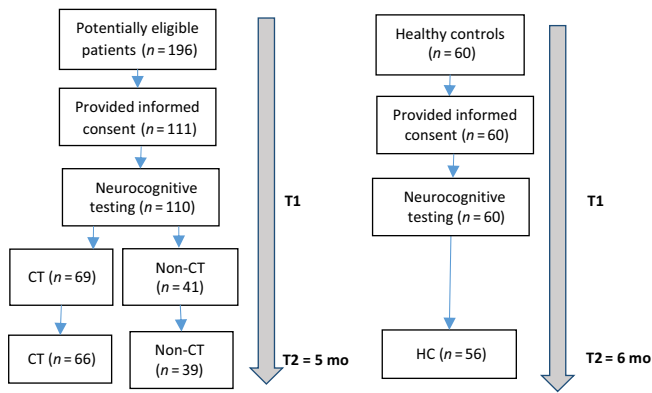
Fig. 1. Flowchart of participants. CT, chemotherapy; mo, months.

group, a second assessment (T2) was performed after the last cycle of CT, but before the start of RT and/or ET. The non-CT group was tested within the same time frame, before the start of adjuvant therapy and 5 months later. The HC group was tested and retested with a 6-month time interval. A standardised neuropsychological battery of approximately 1 hour was administered to each patient in a set order.

Neuropsychological Measures

Verbale Leer-en Geheugen Test

The Dutch version of the California Verbal Learning Test (Verbale Leer-en Geheugen Test – VLGT) is a measure of verbal memory commonly used to assess both learning and memory. The presence of a second list B in the VLGT allows measurement of the effects proactive and retroactive interference (RI) on learning and memory (Wohldmann, Healy, & Bourne, 2008). We retained the total score of list A after five recall attempts, the distraction list B, the immediate recall of A, and the delayed recall after 20 minutes, together with proactive interference (PI) and RI.

D-KEFS Colour-Word Test

The D-KEFS Colour-Word Test (Delis, Kaplan, & Kramer, 2001) is designed to measure executive control of attention by involvement of interference of prepotent responses. The test consists of four trials, the first two consisting of word reading and colour naming and measuring speed of information processing. The third and fourth trials are executive function tasks.

D-KEFS Trail Making Test

The Trail Making Test of the Delis-Kaplan Executive Function System (Delis et al., 2001) assesses set-shifting: the ability to fluently switch between different mental sets. We included all variables: visual scanning, number sequencing, letter sequencing as speed of information processing of the different component skills of this task, and executive function number-letter switching.

Controlled Oral Word Association Test

Verbal fluency was assessed with the Controlled Oral Word Association Test (Benton, Hamsher, & Sivan, 1994), a measure of phonemic and semantic fluency (Miatton, Lannoo, & Vingerhoets, 2004).

Finally, a Dutch version of the *National Adult Reading Test* (NART [Nelson & Willison, 1991]; DART [Schmand, Lindeboom, & Harskamp, 1992]) was administered to obtain an estimation of intelligence.

Statistical Analysis

SPSS Statistics for Windows (version 25.0, IBM Corp., Armonk, NY, USA) was used for descriptive analyses. All other analyses were performed in R (Version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria).

Standardisation of the data set

For interpretation purposes, raw scores of neuropsychological tests were converted into standardised scores based on the mean and standard deviation (SD) of the HC group at T1. Hence, for the HC group at T1, each parameter was distributed with zero mean and SD equal to 1.

Group differences

T2 scores were also standardised based on the mean and the SD of the HC group on T1. This allowed us to then calculate differences between T2 and T1 scores which were based on the same standardisation, thus providing a more direct link with raw differences (as opposed to, for example, T2 corrected for T1). Paired samples t-tests were conducted to compare performance in all neuropsychological measures between HCs and the two patient groups. ESs were calculated as Cohen's d (mean paired differences/SD paired differences). We calculated the difference score (T2 minus T1) and assessed significant differences between the groups. P-values indicated group as a significant predictor. Applying multi-comparison Bonferroni correction, we deemed differences with $p < .001$ as statistically significant. For each test value, groups were compared, and we calculated ES, confidence interval (CI), and p-value. Generally, an ES of .8 or more is considered a large effect, an ES of .5 is considered moderate, and an ES of .2 is considered a small effect.

Regression-Based Change

As previously mentioned, it is important to compare group differences and to determine which subgroups of patients show relevant decline. To detect which subgroup of patients show clinically relevant decline, we used RBC scores (McSweeny, Naugle, Chelune, & Lüders, 1993), which originate from differences in initial baseline scores, considering relevant demographic variables that could influence change in a test–retest situation.

For the different test variables, we calculated optimal regression coefficients by regressing the retest scores for

the HC group against their prior scores (Supplementary Material A). Potential contributing factors, such as age, intelligence, education, and fatigue, were added to the equation, together with sleep quality and menopausal status (Henneghan, Carter, Stuifbergan, Parmelee, & Kesler, 2018; Lord, Buss, Lupien, & Pruessner, 2008). Beginning with performance on T1, the predicting variables were incrementally added until the best model was achieved. T1 score and age were important contributing factors. Following these regression models (Supplementary Material B), we calculated optimal regression coefficients and predicted T2 scores for patients in the CT and non-CT groups.

To determine whether a patient's retest performance significantly deviated from normal expectations, we compared the observed retest score with the regression-predicted retest score and divided the difference by the mean square error. We obtained standardised difference scores that represent to what extent the actual score on T2 deviated from what would be expected based on the T1 score and the change occurring in the HC group. The standardisation of the T2 scores based on the mean and SD of HCs at T1 distributes solely for ability (+ error). However, we argue that degree of change expected in controls is modelled for using the linear regression models. These are oriented towards estimating how much a patient in the control group, given a certain starting ability and demographic factors, should be expected to show practice effects. By contrasting the standardised T2 scores of the experimental conditions against the expected scores based on these models, we thus investigate these groups relative to both ability and practice effects in the control group.

To delineate which participants deviated significantly from their expected T2 scores (and can thus be said to have experienced cognitive decline), it is necessary to set a cut-off point to the RBC scores. The heterogeneity of definitions of impairment makes such conclusions somewhat arbitrary. Given the large differences that exist in the determination of a threshold in previous papers (Schilder et al., 2010), we have decided to include a table detailing the prevalence of 'declined' subgroups in the different conditions for several thresholds. Even though we decided to uphold the standard of choosing 2.5 SD, we agree that placing the boundary at −2.5 SD is a subjective decision (which is why we chose to also include what the 'declined' group would look like following −1.5 SD and −2 SD). We applied the reasoning that if the 'significantly worse performing' group was based on a boundary less than −2.5 SD, this would not follow the restrictions typically placed on determining outliers within a distribution. It might be relevant for other papers to better compare these subgroups to their own threshold selection (Schagen et al., 2006).

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics of both patient groups and HCs are presented in Table 1. From the final sample of 110 patients that completed T1, 69 received adjuvant CT (CT group). Forty-one patients received RT and/or ET (non-CT group). Ninety-six percent of patients in the CT group received the combination of FEC/D. All but one patient (97.6%) in the non-CT group received adjuvant ET, compared to 77% in the CT group. The average age of all women was 49.1 years. Patients in the non-CT group were significantly older, and adjuvant CT was associated with higher cancer stage. Nearly 90% of patients in the non-CT group had a pT1 tumour, while 50.7% of those in the CT group had pT2 breast cancer. Thirty-nine patients in the CT group (56.4%) and 19.5% in the non-CT group had positive lymph nodes. Before treatment, 35%, 54%, and 43% of patients in the CT, non-CT, and HC groups, respectively, were postmenopausal. No significant differences in education and estimated intelligence quotient (IQ) were found. Three patients in the CT group and two in the non-CT group dropped out at T2. In the HC group, 4 of 60 participants dropped out by T2. Thus, complete data were obtained from 105 patients and 56 HCs.

Group Differences in Cognitive Change

Patient groups and controls did not differ in most neuropsychological tests (Supplementary Materials C and D), but a significant difference was found for verbal fluency-letters ($p = .0013$), with a large ES between the CT and non-CT groups (ES = .89, $p \leq .001$) and moderate ESs on verbal fluency-letters between the CT and HC groups (ES = .61, p = .0011) and for VLGT PI between the CT and HC groups (ES = .62, $p \leq .001$). Thus, the CT group showed significant decline on letter fluency and the PI task of the VLGT compared to the other groups.

Cognitive decline versus no cognitive decline

As explained earlier, we systematically selected subgroups of patients with standardised difference scores of −2.5 SD. Using the −2.5 points threshold, the percentages of subjects with cognitive decline were 24.24% (16/66) in the CT group, 15.20% (6/39) in the non-CT group, and 7.14% (4/56) in the HC group (Supplementary Material E). Therefore, the proportion of participants performing lower than expected between T1 and T2 significantly differed between the groups ($\chi^2 = 6.973$, $p = .030608$).

Furthermore, to link this relative decline in cognitive performance to actual differences in neuropsychological measures, we used independent group comparisons for raw scores at T2; observing that the subgroup of participants with cognitive decline had significantly lower raw scores at T2 than those without cognitive decline, especially in the CT group (Supplementary Material F). For all analyses, a *p*-value <.01 was considered statistically significant. The CT group with cognitive decline scored significantly lower than the group without cognitive decline on the VLGT total recall ($p = .0007$), short delay recall ($p = .0029$), long delay recall

Table 1. Disease and demographic characteristics of the sample

Characteristics	Patients scheduled for chemotherapy ($n = 69$)		Patients scheduled for non-chemotherapy treatment ($n = 41$)		Healthy controls ($n = 56$)		One-way ANOVA or Mann–Whitney U-test	
	Mean or count	SD	Mean or count	SD	Mean or count	SD	F-statistic	p
Age at baseline years (range)	46.7 (27–64)	9.7	53.1 (44–65)	5.6	47.9 (25–64)	10.6	7.643	.001
pTNM classification								<.001*
T1	21 (30.4%)		36 (87.8%)		NA			
T2	35 (50.7%)		5 (12.2%)		NA			
T3	12 (17.4%)		NA		NA			
T4	1 (1.4%)		NA		NA			
Positive lymph nodes	39 (56.4%)		8 (17.1%)		NA			<.001*
Menopausal status							.497	.609
Premenopausal	45 (65.2)		19 (46.3%)		32 (57.1%)			
Postmenopausal	24 (34.8)		22 (53.7%)		22 (42.9%)			
Surgical treatment								.001*
Lumpectomy	30 (43.5%)		33 (80.5%)		NA			
Mastectomy	35 (50.6%)		8 (19.5%)		NA			
Radiotherapy								.239
y	65 (94.2%)		36 (87.8%)		NA			
n	4 (5.8%)		5 (12.2%)					
Hormonal therapy								.004*
y	53 (76.8%)		40 (97.6%)		NA			
n	16 (23.2%)		1 (2.4%)					
Education years	13.7	2.9	13.5	2.6	14.5	2	1.968	.114
Estimated IQ	111.4	10.2	112.8	11.4	116.5	10.2	1.492	.228

ANOVA, analysis of variance; IQ, intelligence quotient; NA, not applicable; SD, standard deviation; pTNM, classification of malignant tumours; y-n: yes – no.
*Disease variables between the two patient groups were assessed with the Mann–Whitney U Test; significance values are reported.

($p = .009$), D-KEFS visual scanning ($p = .002$), D-KEFS letter ($p = .0022$), D-KEFS switching ($p = .001$), D-KEFS word reading ($p = .003$), D-KEFS inhibition ($p = .00043$), D-KEFS inhibition/switching ($p = .0006$), and verbal fluency-letter ($p = .0001$) tests. In the non-CT group, there were only significant differences on verbal fluency-animals ($p = .0065$) and profession ($p = .0018$). No statistically significant difference ($p < .01$) was retained between any measures in HCs.

When relating the raw T2 scores to the T1 scores for the groups with and without cognitive decline, results indicated that the group with cognitive decline typically consisted of those who had already lower performance at T1, which remained within the normal range. No statistically significant differences ($p < .001$) between any measures in the non-CT and HC groups with and without cognitive decline were retained at T1. In the CT group, the group that showed 'later decline' performed significantly worse on T1 than the group that did not show later decline in the VLGT total recall ($p = .0015$), short delay recall ($p = .0088$), D-KEFS TM numbers ($p = .0033$) D-KEFS TM letter ($p = .0029$), and D-KEFS TM switching ($p = .0058$) tests. Figure 2 depicts the subtle deterioration of the subgroup already scoring lower at T1.

Finally, patients with and without cognitive decline differed in several features, as summarised in Table 2. Participants with significant cognitive decline had a lower level of education overall, but this was only significant in

the CT group. Patients with cognitive decline were also significantly older in the CT group. Participants with cognitive decline showed lower estimated intelligence, but this was only significant in the non-CT group.

DISCUSSION

The primary focus of this study was to investigate the prevalence of cognitive decline in women with breast cancer immediately after CT, compared to the performance of non-CT treated patients and HCs. Following concerns of previous studies, we attempted to study cognitive decline not through significant deviations from norm scores; however, we focused on ESs in between-group changes using scores standardised based on HC performance. Furthermore, we explored the relevance of discerning an 'at-risk' subgroup, using standardised RBC scores to identify patients with dysfunctional evolutions in their cognitive performance. Thus, we adhered to recent methodological recommendations to evaluate psychometric changes in longitudinal studies (Andreotti et al., 2016).

Group Level

At the group level, results showed several between-group differences. Both CT and non-CT patient groups showed less resistance to PI at T2. In contrast to the findings by Root et al. (2016), performance in the VLGT distraction list opposing

Table 2. Comparison of features in patients with and without cognitive decline

	Group	Decline	No decline	p (*t* test)
Education years	HC	13.2	14.8	
	Non-CT	11	14	0.068
	CT	10.8	14.6	0.0006*
Sleep quality	HC	7.5	7.2	0.414
	Non-CT	7	7,1	0.732
	CT	7	7	0.88
IQ	HC	112	117	0.339
	Non-CT	100.5	115	0.0038*
	CT	106	113	0.089
Age	HC	48.2	47.9	0.9634
	Non-CT	52	53.2	0.837
	CT	53.5	44.6	0.00037*
Days since surgery	HC			
	Non-CT	20	28.5	0.0395
	CT	19.4	19.4	0.9934

CT, chemotherapy; HC, healthy control; IQ, intelligence quotient.
*$p < 0.001$.

the first encoding of list A seemed more difficult in both groups. The shifting of attention while inhibiting learned material caused problems for patients, whereas HCs showed improvement; therefore, patients were less able to inhibit previously learned – distracting – information. These results are comparable with data published by Andryszak in a recent study on verbal memory in CT-treated breast cancer patients compared to HCs (Andryszak, Wiłkość, Żurawski, & Izdebski, 2018). The presence of list B did not otherwise inhibit retrieval of previously memorised material (RI). Comparing CT-treated patients with both non-CT and HC groups, we found large ESs for letter fluency [CT *vs.* Non-CT (ES = .89); CT *vs.* HC (ES = .61)]. In the letter fluency task, patients must maintain instructions in working memory and suppress semantically related words while adapting novel search strategies; this measures verbal and executive control ability. Prior research suggests the effects of CT on specific domains of executive functioning. These findings suggest that CT-treated patients are vulnerable to cognitive control and monitoring (Chen et al., 2014; Yao, Bernstein, & Rich, 2017). Deficits in executive functioning may not have
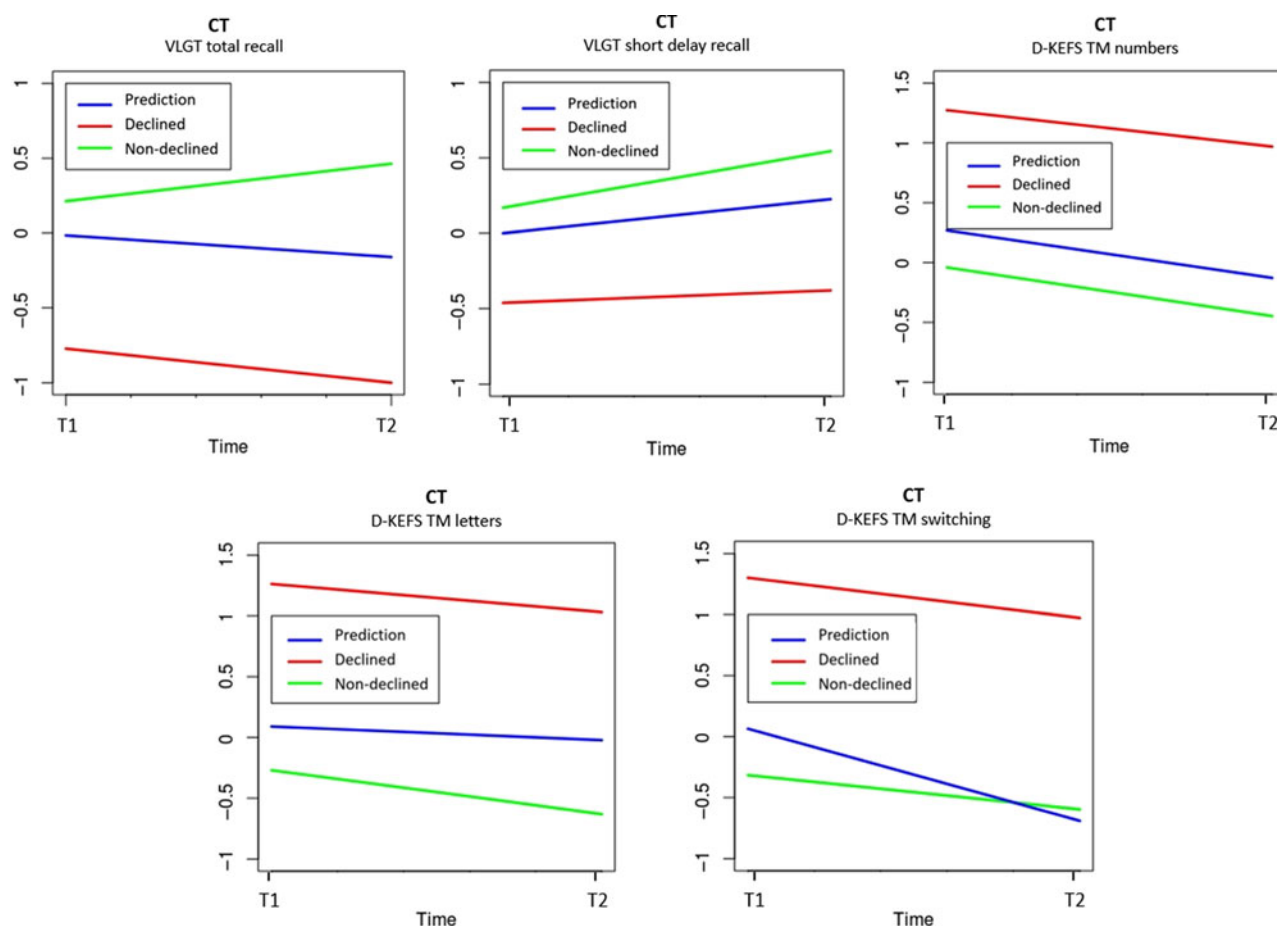
Fig. 2. Visual presentation of declined and non-declined T1 and T2. The prediction line consists of the mean of the total CT group at T1 and the predicted score at T2, the latter on the basis of the expected evolution of the CT group, given their basic score, age, education, and other factors in this study, as well as the evolution of the HC group.

been reflected in the Colour-Word and Trail making task because of a lack of sensitivity in these tests. Moreover, in contrast to these tests, the letter fluency task requires greater effort and a more active strategic search. Regardless of the observation of significant differences on some measures, no other significant group differences were found globally. Despite the reduced performance that was observed in the CT group, the non-CT group also received cancer treatment, such as RT, hormonal therapy, and the additional effects of psychological factors and fatigue (Ahles & Root, 2018; Andreotti et al., 2015; Boele, Schilder, de Roode, Deijen, & Schagen, 2015; Menning et al., 2015) with a potential negative impact. Our findings agree with recent meta-analyses that emphasize the subtlety of cognitive dysfunction, but deviate somewhat from the findings that cognitive impairments in breast cancer patients occur independently of CT (Bernstein et al., 2017; Ono et al., 2015).

Individual Level

We aimed to determine whether a subgroup of patients with cognitive decline could be identified using RBC scores to predict individual performance. We observed a larger subgroup with severe cognitive decline among CT-treated patients, compared to the other groups. Twenty-four percent of patients in the CT group showed scores 2.5 points lower than expected in more than one test at T2, compared to 15% and 7% of those in the non-CT and HC groups, respectively. Lower education level and older age were significant predictors of cognitive decline in the CT group. An association between decline and age could not be found in the other groups. Other researchers demonstrated associations among cognitive performance, age, and years of education, with a larger effect in CT-treated patients than in non-CT-treated patients (Ahles & Hurria, 2018; Tager et al., 2010). Dichotomisation of patients into those with and without cognitive decline could have concealed the fact that all CT-treated patients experience negative cognitive effects; however, only patients with lower IQ and education were unable to maintain task performance, whereas younger patients with higher education were more resilient to decline.

Study Limitations

This study had several limitations. First, a number of patients declined to participate, mainly because of the burden of the given diagnosis at that time. Second, all participants were white and Flemish, the majority of whom were highly educated and financially stable, limiting the external validity of the findings. Given the small number of included participants, a further limitation is that the study may have been underpowered to identify predictors of cognitive decline within subgroups. Fourth, we evaluated the acute, short-term effects of CT; we did not include the analysis of long-term cognitive performance of the patient groups. And finally, in this paper, we did not include an assessment of perceived

cognitive decline nor of any other possible contributing psychological factors. Since mechanisms that cause cognitive decline in breast cancer patients are likely to be multi-factorial, these factors may increase vulnerability to cognitive deterioration and should be considered for future research.

Clinical Implications

The results corroborate the hypothesis that CT is an important factor in cognitive decline in breast cancer patients. The findings of this study can alert healthcare professionals of the need to identify and support breast cancer patients with potential decline, thereby facilitating targeted rehabilitation after treatment for breast cancer. The findings also emphasise that healthcare professionals and researchers should carefully use terms such as 'impairment' and 'dysfunction'. There is a need to agree on a definition of cognitive decline and standardise the methodology for accurate assessment, thus allowing comparison of studies regarding the prevalence and nature of cognitive dysfunction in patients who have undergone treatment for cancer.

Future Studies

The possibility that psychological factors increase vulnerability for cognitive decline after cancer treatment remains controversial (Vearncombe & Pachana, 2009). Core executive functions, such as task-switching and inhibition, are essential for task performance, but also serve self-regulatory abilities. Berman et al. (2014) showed that pre-treatment worry was associated with cognitive impairment; other research has linked the lack of cognitive control to a higher tendency to ruminate (De Lissnyder, Koster, Derakshan, & De Raedt, 2010). Further research is needed to determine whether cognitive function and perseverative cognitions share common factors.

Finally, the tendency to objectify cognitive complaints after cancer resulted in a neglect of subjective experience. Qualitative studies addressing the phenomenology of cognitive difficulties are limited but can only enrich and complement existing research.

To conclude, our findings revealed no significant global difference in performance between CT- and non-CT-treated participants, aside from cognitive control and monitoring frailty in verbal fluency letters and PI performance. Seventy-five percent of patients in the CT group continued to perform normally; however, compared with HCs, a significantly larger subgroup of participants with cognitive decline could be discerned. In particular, those who already performed more weakly before adjuvant treatment and with lower education levels and higher age were prone to further deterioration in performance; they constituted a vulnerable group. We should, however, not disregard the fact that neuropsychological assessment may not be sufficiently sensitive to capture the complexity of cognitive problems in cancer

survivors and that patient-reported outcomes should be incorporated into such assessments.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/S1355617720000296

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