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NeuroCog FX study: A multicenter cohort study on cognitive dysfunction in patients with early breast cancer

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Abstract

Objective: Complaints about cognitive dysfunction (CD) reportedly persist in approximately one third of breast cancer patients, but the nature of CD and possible risk factors are unknown.

Methods: A cross-sectional, multicenter study was set up at 9 German oncological rehabilitation centers. Objective cognitive performance was assessed by the NeuroCog FX test, a short computerized screening (duration <30 minutes) which assesses working memory, alertness, verbal/figural memory, and language/executive. Patients' test performance was correlated with treatment factors (chemo-, radiotherapy), subjective performance (FEDA), depression (PHQ-9), quality of life (EORTC QLQ-30), and clinical characteristics.

Results: From February 2013 to December 2014, a clinically homogenous sample of 476 patients was recruited (early tumor stage [T0-T2]: 93%; node-negative: 67%; chemotherapy: 61%; radiotherapy: 84%). NeuroCog FX could be administered in 439 patients (92%; median age: 50 [24-62] years). Patients showed decreased performance in attentional-executive functions (but not verbal/figural memory) and a 3-fold rate of CD in terms of below average performance in at least 1 cognitive domain (42%). Approximately 40% of the patients also reported subjective cognitive impairment (FEDA). No therapy-specific effect on test performance was obtained in the NeuroCog FX test.

Conclusions: Breast cancer survivors showed objective attentional-executive and subjective cognitive impairments. No therapy-specific adverse side effect on objective cognitive performance was found. Depression strongly contributed to objective and subjective cognitive complaints and reduced quality of life.

KEYWORDS

breast cancer, chemotherapy, cognitive adverse side-effects, cognitive dysfunction, computerized cognitive screening, neuropsychological assessment, oncology

1 | BACKGROUND

Cognitive dysfunction (CD) in terms of attention and memory impairment is often self-reported by cancer patients. Depending on the tumor entity, a prevalence of 16% to 75% is assumed.[1] Cognitive dysfunction particularly affects women after breast cancer, is often prevalent before the start of cancer treatment, and is mediated by cancer-related post-traumatic stress.[2] After chemotherapy, a deterioration of

cognitive function is frequently reported by patients, and subjective impairment persists in 15% to 45% of the patients. In general, it is assumed that cognitive deficits are related to the anti-tumor treatment.[3-5] However, impaired cognition seems to be a complex issue in cancer patients. In fact, it has been demonstrated that other factors such as depression, anxiety, and fatigue play an important role.[6] In addition, subjectively perceived poor quality of life is correlated with impaired cognitive function.[7,8]

So far, cognitive deficits could only be objectified reliably on the basis of extensive neuropsychological assessment batteries.[6,9] However, such time-consuming procedures are usually not suitable for clinical routine thus limiting their applicability in clinical studies. Therefore, the computerized NeuroCog FX test has been used in the current study. This is a quick, validated cognitive screening tool that is composed out of 8 subtests addressing 4 cognitive domains, namely working memory, alertness, recognition memory, and language.[10]

The present multicenter study was initiated to explore and identify possible risk factors especially the impact of chemotherapy for cognitive deterioration in patients with early or locally advanced breast cancer who participated in a rehabilitative inpatient program.

2 | METHODS

This study was a non-interventional prospective, multicenter, stratified cohort study. Stratification was performed according to the nodal status and whether or not chemotherapy was completed. The primary endpoint of the study was to correlate objective and subjective cognitive performance with clinical characteristics in particular chemo- and/or radiotherapy and nodal status. The study was approved by each participating institution's Research Ethics Board (Medical Association of Hessen, Germany, reference number FF 124/2011).

2.1 | Patients

Between February 2013 and December 2014, patient recruitment involved 9 oncological rehabilitation hospitals in Germany. The usual duration of inpatient rehabilitation programs in these centers was 3 weeks. Among the rehabilitative units, cognitive screening was handled variably and was optional. The rehabilitative treatment was adapted to the individual patient problems and included physical activities, information to dietary changes, and, if necessary, psychooncology treatment and web-based cognitive training. Immediately after admission, eligible patients were invited to enroll in the study. Patients who provided informed consent were reported to the leading study center (ie, Clinic Reinhardshöhe).

Inclusion criteria were as follows: employable age between 18 and 62 years; presence of early or locally advanced primary breast cancer; post-surgery, completion of neoadjuvant or adjuvant chemotherapy and/or radiotherapy. No patients were under chemo- or radiotherapy. An existing endocrine therapy or immune therapy with trastuzumab was allowed. Exclusion criteria were defined as follows: locally recurrent or metastasized disease; incomplete primary treatment; radiotherapy of the CNS; neurological or psychiatric conditions including addictive disorders (eg, drug abuse); administration of psychoactive or neuropharmacological substances (in particular opioids, benzodiazepines or antiepileptic drugs); strong visual impairment; lack of understanding of the German language; and inability to complete psychometric questionnaires or to operate a computer keyboard without assistance.

During the first week of the rehabilitation program, cognitive performance, health-related quality of life, and mood (ie, presence of depression) were measured by the following validated psychometric instruments:

2.2 | Measures

The NeuroCog FX test, a German computerized cognitive screening tool for serial examinations of patients with epilepsy and other neurological diseases, was developed to fill the gap between unspecific rating scales and comprehensive neuropsychological assessments.[10] The test duration is less than 30 minutes. The test is well suited for administration by non-academic personnel at multiple sites. Eight subtests address 4 cognitive domains: working memory (Digits, 2-back), attention (Simple Reaction, Go/No Go, Inverted Go/No Go), memory (Verbal and Figural Memory), and language/executive (Phonemic Fluency). Normative data were obtained from healthy subjects (n = 244, age range = 16-75 years; retest: n = 44; validation: n = 40). Psychometric analyses confirmed sufficient reliability and concurrent validity, particularly in patients with cognitive deficits. NeuroCog FX memory and overall performance scores also showed "fair" to "good" diagnostic utility with respect to deficits revealed by established tests. NeuroCog FX thus provides reliable and valid measures of cognitive performance and may be used in clinical and research contexts as a cognitive screening instrument.[10] Age-adjusted standard values (mean 100, standard deviation 10) are available for 4 different age groups (16-29, 30-44, 45-59, 60-75 years). Besides the subtest scores, age-adjusted standard scores are also calculated for each cognitive domain (ie, working memory, alertness, memory, and language) and for speed (averaging 3 reaction-time based tests), quality (averaging number-of-correct-responses based tests), and overall performance (all tests).

The *Patient Health Questionnaire (PHQ-9)* addresses depression and provides a categorized 5-stepped sum score (0-4: minimal, 5-9: mild, 10-14: moderate, 15-19: moderately severe, 20-27: severe) and an indicator for major depression.[11]

The *Questionnaire on Experienced Deficits of Attention (FEDA)* provides normative scores for 3 dimensions of subjective performance in daily life (mental processes, practical activities, drive/power).[12]

Finally, the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30, version 3)* addresses health-related quality of life and functioning.[13] For clinical evaluation, we applied normative data from German healthy female controls.[14]

2.3 | Statistical analysis

Standard scores below 85 (ie, mean minus 1.5 standard deviations) were generally considered as "below average". For the statistical test of group effects, we used the non-parametrical Mann-Whitney and the χ^2-test, and for testing bivariate correlations we used Spearman's

rank correlation. Effect sizes of significant group effects were estimated with Hedges' g (weak: $0.2 < |g| \leq 0.5$; medium: $0.5 < |g| \leq 0.8$; strong: $|g| > 0.8$) while effect sizes of significant correlations were evaluated by established criteria (weak: $|r| > 0.2$; medium: $|r| > 0.3$; strong: $|r| > 0.5$).[15] Data analysis was performed with IBM SPSS 23 (IBM Inc.).

A priori power analysis with the G*Power software (version 3.0.8) was chosen.[16] An a priori power analysis for a 2 groups *t* test required a decision between a 1-tailed and a 2-tailed test, a specification of effect size measure d under H_1, the significant level α, the required power (1-β) of the test, and the preferred group size allocation ratio n_2/n_1. The test revealed that a sample size of $N = 500$ patients (including an anticipated maximum dropout rate of 20%) would be required to have an 80% chance for a significant finding ($P < 0.05$) if the rate of cognitive deficits between patients with versus without chemotherapy actually differs for at least 30% (χ^2-test).

3 | RESULTS

3.1 | Patient characteristics

In total, 476 patients with early or locally advanced breast cancer were included. The patient characteristics are detailed in Table 1. All chemotherapy treated patients received further radiotherapy, and 110/476 patients (23%) were treated with adjuvant radiotherapy only. At study entry, all patients had completed chemotherapy or radiotherapy.

The NeuroCog FX Test was administered in 439 out of 476 patients (92%), thus surpassing the sample size requirement obtained from a priori statistical power analysis. Thirty-seven patients (8%) were not investigated because they rejected the test, the test could not be performed due to technical problems, or for other reasons not further specified.

3.2 | Cognitive performance

The NeuroCog FX test showed 33% of patients ($n = 145$) with cognitive abnormality in one, 32 patients (7.3%) were impaired in 2, and only 5 patients (1.2%) in 3 or 4 subtests. By contrast, 257 patients (58,5%) showed no CD in the objective test battery.

The median standard scores from the FEDA were 1 standard deviation below the normative mean (focus and speed of mental processes: 89.1 [range: 26-119]; energy and speed of practical action: 89.6 [range: 19-113]; drive/power: 91.6 [range: 33-117]) and more than one third of the patients showed "below average" standard scores (42.2%, 40.5%, 35.1%, respectively) indicating subjective cognitive deficits in many breast cancer patients. Positive correlations between subjective and objective cognitive performance were weak (<0.3) but found for almost all parameters from FEDA and NeuroCog FX.

3.3 | Health-related quality of life

Table 2 shows the group mean standard scores from the EORTC QLQ-30 of our patients (normative data from 448 healthy controls).[14] Quality of life and physical functioning were 1 standard deviation below healthy female controls, and cognitive functioning was almost 3 standard deviations below controls; the other functional scales (role, emotional, social) were 2 standard deviations below controls.

TABLE 1 Patient characteristics ($n = 476$)

Age (years) [a]	**50 [24 – 62]**
Tumor size	
- T0	18 (4%)
- Tis	36 (8%)
- T1	265 (55%)
- T2	123 (26%)
- T3	14 (3%)
- T4	9 (2%)
- Unknown	11 (2%)
Nodal status	
- Positive	148 (31%)
- Negative	317 (67%)
- Unknown	11 (2%)
Hormone receptor status	
- Positive	375 (79%)
- Negative	90 (19%)
- Unknown	11 (2%)
Her2-neu status	
- Positive	94 (20%)
- Negative	359 (75%)
- Unknown	23 (5%)
Local treatment	
- Breast-conserving surgery	364 (76%)
- Mastectomy	102 (22%)
- Unknown	10 (2%)
Node dissection	
- Sentinel lymph node biopsy	357 (75%)
- Axillary lymph node dissection	77 (17%)
- None	32 (6%)
- Unknown	10 (2%)
Radiotherapy	
- Yes	400 (84%)
- No	66 (14%)
- Unknown	10 (2%)
Chemotherapy	
- Yes	290 (61%)
- No	177 (37%)
- Unknown	9 (2%)
Cytostatics	
- Anthracycline	266 (56%)
- Taxane	244 (51%)
- Platinum	16 (3%)
Hormonal therapy	
- Yes	345 (72%)
- No	121 (26%)
- Unknown	10 (2%)
Interval chemotherapy/start – NeuroCog FX (months) [a]	10 [4 – 213]

[a]Median and range.

[b]$n = 443$.

TABLE 2 Quality of life of our patients in contrast to EORTC QLQ-30 normative data from healthy subjects (n = 448)[14]

Scales	MSS	SD
Global health/quality of life	90.54	(9.83)
Physical functioning	88.89	(12.51)
Role functioning	82.68	(13.56)
Emotional functioning	83.33	(14.71)
Cognitive functioning	72.64	(20.21)
Social functioning	.79.42	(17.01)

MSS, mean standard score; SD, standard deviation.

All scales of the EORTC QLQ-30 correlated with the alertness and memory domain scores as well as the speed, quality, and overall total scores of the NeuroCog FX. In addition, Role Functioning and Social Functioning were correlated with the language domain score, while Physical Functioning was significantly correlated with all 4 cognitive domains. The EORTC Fatigue scale was correlated with the overall standard score from the NeuroCog FX as well as standard scores from simple reaction, inverted go/no go, verbal memory, and phonetic fluency. All correlations were weak (r < 0.3).

3.4 | Depression

Patients who currently suffered from a diagnosed psychiatric condition were excluded from the present study. Nevertheless, PHQ-9 indicated "major depression" in 69 out of 476 patients (14.5%), and the categorized PHQ-9 total sum was "moderately severe" or "severe" in 13.4% (n = 64) of the patients. The depression score was negatively correlated with NeuroCog FX performance in the 3 alertness subtests and the verbal memory subtest, the alertness and memory domains, and speed, quality, and overall total scores.

Of note, depression showed strong negative correlations with subjective cognitive performance (FEDA – mental: r = –.757, practical: r = –.738, drive/power: r = –.762) and health-related quality of life (EORTC QLQ-30 – Global Health Status: r = –.612, Physical Functioning: r = –.544, Role Functioning: r = –.488, Emotional Functioning: r = –.714, Cognitive Functioning: r = –.691, Social Functioning: r = –.561) with P < .001 for all reported correlations.

3.5 | Impact of clinical factors

We found no effect of treatment factors or nodal status on any measure of objective cognitive performance, ie, subtest, domain or total scores of the NeuroCog FX. In particular, we found no effect of chemotherapy or radiotherapy (Table 3). Patients with versus without chemotherapy also showed the same number of subtests with below average performance (χ^2-test, P = .641; data not shown); recency of chemotherapy might play a role for cognitive outcome, but we found no correlation between any of the NeuroCog FX parameters and the length of the interval between start of chemotherapy and time of cognitive assessment. For the only exception, the Simple Reaction subtest, the correlation was even negative, indicating faster reaction times in patients with shorter chemotherapy-to-assessment intervals. Finally, we found no effects of combined chemotherapy and radiotherapy (data not shown). Thus, despite sufficient statistical power, this study found no evidence for increased cognitive deterioration in patients who underwent chemotherapy as compared with patients with other therapies.

By contrast, chemotherapy but not radiotherapy had a negative impact on patient-reported attention deficits as obtained by the FEDA

TABLE 3 Effects of clinical factors on objective cognitive performance (n = 434)

	Chemotherapy				Radiotherapy				Nodal Status			
	Ctx + (n = 271)		Ctx – (n = 163)		Rtx + (n = 377)		Rtx – (n = 56)		Nodal + (n = 138)		Nodal – (n = 294)	
NeuroCog FX®	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
Digits	96.3	10.6	96.6	10.2	96.3	10.5	97.5	10.1	96.7	10.8	96.3	10.3
2-back	102.4	21.0	99.9	22.6	101.3	21.9	102.7	19.9	104.3	22.1	100.2	21.4
Simple reaction	89.4	16.2	88.0	17.2	88.6	16.3	90.1	18.3	**92.2**	**14.3**	**87.3**	**17.3**
Go/no go	89.2	16.9	88.7	18.4	89.0	17.4	89.0	17.9	**91.9**	**16.4**	**87.6**	**17.8**
Inverted go/no go	92.6	14.5	91.9	14.9	92.5	14.7	91.3	14.0	**95.0**	**12.9**	**91.2**	**15.3**
Verbal memory	100.2	12.2	99.7	11.6	99.9	12.4	101.3	8.7	101.4	11.8	99.4	12.1
Figural memory	103.1	6.5	103.2	5.6	103.0	6.1	103.8	6.5	103.4	6.3	103.0	6.1
Phonemic fluency	102.5	14.7	102.1	14.2	102.1	14.6	104.4	14.2	102.6	15.5	102.1	13.9
Working memory	99.0	13.0	97.9	14.0	98.4	13.4	99.6	12.9	100.2	13.6	97.8	13.2
Alertness	89.3	14.7	88.3	16.0	88.9	15.1	89.2	15.9	**91.6**	**14.2**	**87.7**	**15.5**
Memory	101.9	7.7	101.4	7.6	101.6	7.8	102.7	6.6	102.8	7.3	101.2	7.8
Language	102.5	14.7	102.1	14.2	102.1	14.6	104.4	14.2	102.6	15.5	102.1	13.9
Speed	89.3	14.7	88.3	16.0	88.9	15.1	89.2	15.9	**91.6**	**14.2**	**87.7**	**15.5**
Quality	101.1	8.4	100.3	8.3	100.6	8.5	102.1	7.4	101.8	9.1	100.3	8.0
Overall	98.1	7.9	97.2	8.2	97.6	8.1	98.9	7.4	**99.2**	**8.4**	**97.1**	**7.8**

Ctx, Chemotherapy; Rtx, Radiotherapy; M, mean (100); SD, standard deviation (10). Higher NeuroCog FX® scores indicate higher performance. Significant group effects are printed in bold (Mann-Whitney tests, P < .05). Hedges' g indicated small effect sizes for all effects (|g| < 0.30).

and the EORTC QLQ-30 questionnaire (data not shown). However, Hedges' g again indicated small effect sizes for all obtained effects (|g| < 0.3). We found no effect of chemotherapy or radiotherapy on depression as measured by the PHQ-9 (total sum, categorized total sum, major depression indicator). Thus, the chemotherapy effect on subjective cognitive functioning was probably not mediated by depression.

As regards other clinical parameters, node-positive patients showed decreased Physical and Role Functioning in the EORTC QLQ-30, but, unexpectedly, better performance in the 3 alertness subtests and, thus, better speed and overall total scores in the NeuroCog FX (Table 3). However, Hedges' g for these effects again indicated small effect sizes (|g| < 0.4).

4 | DISCUSSION

The present study is one of the largest investigations on cognitive performance in patients with early or locally advanced breast cancer. More than one third of the patients (42%) were affected by an objective cognitive deficit in terms of clearly below average performance in at least 1 cognitive subtest in the NeuroCog FX Test. However, we found no statistically significant effects of clinical parameters (chemo-, radiotherapy, nodal status) on cognitive functions. Our findings ranked in a comparable dimension of previous data from other studies.[1-4,17] For example, in a comparative cohort study in patients with non-metastatic colorectal cancer (n = 289), which also used a computer-assisted neuropsychological test battery, the rate of objective cognitive deficits 1 year after completion of tumor therapy was 46% as compared with 13% in healthy controls; these rates are almost identical to the rates as obtained in our study.[17]

Despite sufficient statistical power and using validated sensitive measures of objective cognitive performance, our study could not confirm any specific effect of the preceding therapy on cognition several weeks thereafter. Neither chemotherapy, nor radiation therapy, nor the patient's nodal status had a negative impact on test performance.

This finding is in contrast to previous studies or meta-analyses that reported a relation between chemotherapy and cognitive deterioration. We suppose that the low number of cases in these studies together with a possible negative patient selection bias and higher clinical heterogeneity of the patient collective might explain this difference.[18,19] In addition, meta-analyses on this issue sometimes referred to different neuropsychological test batteries with questionable comparability.[8]

In contrast to normative data from EORTC QLQ-30 from healthy controls, our study population showed lower results in terms of general quality of life, physical and cognitive functioning as well as other functions (role, emotional and social).[14] However, in our patients reported cognitive scores and fatigue score, ie, EORTC QLQ-30 fatigue symptom scale, were only weakly correlated with objective test scores but showed strong negative correlations with depression (PHQ-9). This finding is highly consistent with findings from a recent large study which compared non-metastatic breast cancer patients (n = 581), who received chemotherapy, with age-matched non-cancer controls (n = 364) on self-reported cognitive performance (measured by the Functional Assessment of Cancer Therapy-Cognition, FACT-Cog).[20] As compared with controls, breast cancer patients reported significantly more subjective cognitive deficits from pre-chemotherapy to the 6-month follow-up and depression was significantly associated with lower FACT-Cog total scores.

Our patients who underwent chemotherapy as compared with other therapies self-reported slightly more deficits and decreased cognitive functioning while no therapy-specific effects on self-reported performance were reported by Janelsins et al.[20] Furthermore, a nocebo effect of informing patients about possible cognitive side-effects of cytotoxic agents on subjectively perceived cognitive performance has been shown.[21]

Post-traumatic stress after surviving breast cancer can affect the psychological condition of patients in individually different ways.[22] In fact, 15% of our patients showed an indication of major depression which had not been diagnosed yet, and depression strongly contributed to reduced health-related quality of life. We found only weak correlations with objective cognitive performance consistent with the notion of no or mild cognitive alterations in depression.[23]

Several features of the present study support the validity of our findings. The patients from our sample formed a largely homogeneous collective as tumor states had limited variance and metastasized or relapsed patients were excluded. Furthermore, patients with diagnosed neurological or psychiatric conditions or subjects taking psychoactive drugs were excluded. Also, the median age of the patients was younger than in comparable studies which reduced the risk of including patients with incipient or manifested dementia or reduced cognitive reserve capacity. The NeuroCog FX has previously been used in several studies and was shown to provide reliable and sensitive measures of cognitive deterioration.[24-26] Finally, the study was sufficiently powered to find clinically relevant effects.

4.1 | Clinical implications

The results of the NeuroCog FX study have major clinical implications. First, health care professionals should inform their patients with breast cancer that CD could occur independently from chemotherapy and or radiotherapy. Second, perceived cognitive deficits have broad implications for the well-being of breast cancer survivors. Finally, a greater understanding of cognitive impairment in breast cancer patients may lead to the development of effective treatment of CD.

4.2 | Study limitations

Only patients having gone through an in-patient rehabilitation program and at a single time-point were included in the study. In contrast to other countries, in Germany more than 70% of patients with breast cancer take advantage of oncological rehabilitation. Moreover, we assume, oncological rehabilitation has been predominantly used by patients with CD. Despite this fact, we found no negative effects of clinical parameters on cognitive functions. Patients with subjective CD were treated with web-based cognitive training, we postulated however, that a 3-week duration is too short to measure a relevant effect. In our opinion, these facts do not represent a selection bias

and have neither influenced the results. The study was conducted at a single time-point and cross-sectional, ie, no pre-diagnosis or pre-treatment data on cognitive function were available. For the same reason, we could not perform any follow-up investigations using the NeuroCog FX. Unfortunately, we have no data of education level or number of years of education in our study patients. Therefore, we cannot serve with a correlation between education and CD.

5 | CONCLUSION

In summary, by administering the NeuroCog FX, we found objective and self-reported cognitive impairment in 42% of breast cancer patients. No evidence for therapy-specific adverse side effects on objective cognitive performance was obtained, but self-reported deficits were slightly increased after chemotherapy. Objective and subjective measures showed significant correlations with depression and were correlated with self-reported performance, ie, fatigue symptoms. Our findings underscore the utility of a systematic screening for objective cognitive deficits, subjective impairments, and depression in clinical routine.

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ETHICS APPROVAL

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

DISCLOSURE

None declared.

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