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National Institute on Aging /Alzheimer's Association criteria for Mild Cognitive Impairment applied to chemotherapy treated breast cancer survivors

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Abstract

Background—In this analysis we use the National Institute on Aging/Alzheimer's Association (NIA/AA) criteria to identify Mild Cognitive Impairment (MCI) in a sample of breast cancer survivors treated with chemotherapy.

Methods—Sixty women ages 39–79 on a prospective clinical trial of donepezil were assessed at baseline using a battery of standardized/validated neurocognitive measures. Cognitive status was adjudicated to identify MCI by a panel of dementia experts.

Results—Fifty percent were not cognitively impaired, 43% met the NIA/AA criteria for MCI, 2% had dementia, and 5% could not be classified.

Discussion—In this sample, nearly half of breast cancer survivors met the NIA/AA criteria for MCI. We propose these criteria be used to define cancer-related Mild Cognitive Impairment (cMCI), providing a framework for conducting additional studies to further characterize cMCI and identify clinical, imaging, and genetic factors associated with the progression of cMCI to more advanced stages of cognitive impairment.

Keywords

Breast cancer; Chemotherapy; Dementia; Mild Cognitive Impairment; Quality of life; Survivorship

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Introduction

In the United States, there are 13.7 million cancer survivors, 22% of whom are affected by breast cancer [1]. Cognitive dysfunction has been reported to occur in 17% to 75% of breast cancer patients treated with chemotherapy [2–7]. Among patients, “chemobrain,” a term commonly used by cancer survivors to describe problems with their cognitive function, is a feared complication of cancer treatment. Cognitive symptoms may linger indefinitely and adversely affect family relationships, education, career opportunities, and overall quality of life [2]. The number of survivors with lasting effects of chemotherapy will likely continue to grow with improvements in the diagnosis and treatment of breast cancer.

To adequately address this growing problem, standardized diagnostic criteria are needed to replace inconsistent definitions of cognitive dysfunction that exist in published retrospective and prospective studies of cognitive function in chemotherapy-treated breast cancer survivors. In the field of dementia research and clinical care, a system to define and classify cognitive impairment has been well documented and validated. Mild Cognitive Impairment (MCI) is a well-recognized condition marked by symptoms that precede dementia, sometimes by many years.

The clinical criteria to identify MCI, first provided by Petersen et al. and more recently revised by the National Institute on Aging (NIA) and the Alzheimer’s Association (AA), include: (1) memory concerns reported by the patient or an informant; (2) objective evidence of impairment in one or more cognitive abilities such as memory, attention, executive function, language, and visuospatial skills, given age and education level; (3) functional independence maintained with only minor inefficiencies; and (4) not demented [8]. In population-based studies, the estimated prevalence of MCI ranges from 10–20% in persons older than 65 years of age [9–14]. Longitudinal studies demonstrate that individuals with MCI have a 5–15% annual rate of progression to early stage dementia as compared to the general population in which the likelihood of developing dementia is 1–2% per year [15, 16].

The purpose of this study was to apply the NIA/AA criteria for MCI to a cohort of chemotherapy-treated breast cancer survivors with self-reported cognitive dysfunction.

Methods

Patient Population

Research (Wake Forest National Cancer Institute Community Oncology Program (NCORP)) Research Base protocol 97211 was a phase II randomized, double-blind, placebo-controlled clinical trial estimating the efficacy and feasibility of administering donepezil, an acetyl cholinesterase inhibitor, to chemotherapy treated female breast cancer survivors. Eligibility criteria included prior treatment with ≥ 4 cycles of cytotoxic adjuvant chemotherapy for the treatment of invasive breast cancer 1 to 5 years prior to enrollment, and subjective cognitive problems. Additionally, a Karnofsky Performance Status (KPS) ≥ 60 or Eastern Cooperative Oncology Group (ECOG) Performance Status PS of 0–2 was required. Participants taking

anti-estrogen therapy must have been on the same agent for at least 3 months prior and were expected to continue for the duration of the study.

Women taking psychotropic medications (anxiolytics, anti-depressants, sleeping aids, and/or narcotics) were eligible to participate provided they were on a stable dose. The use of cognition-enhancing drugs (e.g, donepezil, memantine, and methylphenidate) was not allowed during the four weeks prior to enrollment or during the study.

Women with a history of metastatic breast cancer or dementia were excluded from the study. Further exclusion criteria included:

1. Ongoing ketoconazole or quinidine;
2. Hypersensitivity to donepezil;
3. Use of investigational medications within the previous 30 days.
4. Multiple sclerosis.
5. Recent myocardial infarction, stroke, or traumatic brain injury.
6. History of substance abuse, schizophrenia, or psychosis.
7. Untreated current severe depression (depression was permitted if treated and stable).
8. Acute severe fatigue, chronic fatigue syndrome, fibromyalgia.
9. History of hepatic or renal dysfunction.

The study (NCT 01466270) was approved by the Institutional Review Board (IRB) at Wake Forest University School of Medicine (Winston Salem, NC) and at the IRBs at the participating sites. All participants gave written, informed consent. The study was opened at 15 Community Clinical Oncology Programs (NCORPs) affiliated with the NCI-approved Wake Forest University NCORP Research Base.

Design/Measures

The purpose of this secondary data analysis was to apply NIA/AA criteria to identify MCI among chemotherapy-treated breast cancer survivors. The NIA/AA criteria for MCI, adapted for this study, are as follows:

1. Subjective cognitive complaint
2. Demonstrated cognitive deficit in at least 1 cognitive domain on standardized measures of cognitive performance (i.e., test scores 1.5 or more standard deviation units below normative data)
3. Cognitive deficit does not cause significant functional impairment in instrumental activities of daily living (i.e., driving, managing medications and finances, and cooking, housekeeping, and laundry)
4. No medical or psychiatric causes account for deficits and impairments
5. Not demented

Subjective cognitive complaints were measured with the Functional Assessment of Cancer Therapy-Cognition (Version 3) (FACT-Cog), a validated self-report questionnaire with excellent test-retest reliability that assesses perceived cognitive functioning and impact on quality of life over the past 7 days [17–19]. The FACT-Cog is composed of four subscales with lower scores indicating poorer functioning: Perceived Cognitive Impairments (PCI) (range: 0–80), Perceived Cognitive Abilities (range: 0–27), Impact on Quality of Life (range: 0–16), and Comments from Others (range: 0–16). A PCI sub-score of <63 was required for enrollment into the study.

Cognitive functioning was evaluated with a battery of validated and standardized objective measures of memory, attention, language, visuomotor skills, processing speed, and motor dexterity administered by a trained and certified examiner. Test score performance falling 1.5 standard deviation units below expected values (based on demographically appropriate norms in non-cancer comparison groups) in one or more cognitive domains was considered evidence of significant cognitive impairment. The Hopkins Verbal Learning Test-Revised (HVLT-R) was used to assess verbal learning and memory [17] and includes Total Recall (TR, sum of 3 learning trials), Delayed Recall (DR, recall following a 20 minute delay), and Savings (% S, [DR/highest learning trial score] × 100). Verbal fluency was evaluated with the Controlled Oral Word Association (COWA) [18]. The Trail Making Test-Parts A and B were administered to assess attention and psychomotor speed (TMT-A) and executive function (TMT-B) [19]. The modified Rey-Osterreith Complex Figure (ROCF) assessed visual-constructional ability (RF-Copy) and immediate (RF-IR) and delayed visual recall (RF-DR) [15,20]. Working memory and concentration were measured with the Digit Span test (DS), a subtest of the Wechsler Adult Intelligence Scale-III [21]. The Grooved Pegboard (GP) measured motor speed and dexterity for the dominant hand (GP-D) and the non-dominant hand (GP-ND) [22].

Self-report questionnaires were administered to evaluate mood, functional status, and quality of life. Global health related quality of life was measured with the SF-36.[23] Fatigue was assessed with the PROMIS 7-item Fatigue scale and the FACIT-Fatigue Subscale, sleepiness with the Epworth Sleepiness Scale, and mood with the Beck Depression Inventory and Beck Anxiety Inventory. [23–27] Functional impairment was judged to be absent if participant responses to the FACIT-Fatigue item, “I am able to do my usual activities” were ‘somewhat’, ‘quite a bit’ or ‘very much’. Significant medical and psychiatric comorbidities and pre-existing dementia were ruled out based on the previously described exclusion criteria.

Adjudication of cognitive status to identify MCI using NIA/AA diagnostic criteria was completed as follows. A panel of four experts in the diagnosis of MCI and dementia (three neuropsychologists, one geriatrician) was assembled. The cognitive function, mood, functional status, and quality of life data for each participant were provided to two adjudicators, who independently reviewed and classified the individual as being cognitively normal, having MCI, or being demented. Disagreements were handled by assignment of a third ‘tie breaker’ adjudicator. Participants who met criteria for MCI were then sub-classified as having amnestic MCI (affecting memory) or non-amnestic MCI (affecting one or more non-memory domains).

Results

Patient Characteristics

Sixty two participants (60 with complete baseline data) from 15 participating sites enrolled in the donepezil *vs.* placebo study between 7/2012 and 1/2013. The primary study results have been reported previously [28]. Participants had a median age of 56 years, were primarily white (90%), married (71%) and had greater than high school education (79%) (Table 1). Eighty seven percent of the cohort was overweight or obese. Most were 12–36 months post-chemotherapy (61%), peri- or postmenopausal (95%) and receiving anti-estrogen therapy (68%), either tamoxifen or an aromatase inhibitor. Participants received the following cytotoxic drugs: cyclophosphamide (71%), doxorubicin (53%), paclitaxel (41%), and/or carboplatin (29%). Nearly all patients received two or three drugs for a median of 4 cycles. Median time from treatment to study enrollment was 27months.

Cognitive function

This sample showed poorer mean performance compared to normative data for each cognitive measure except immediate and delayed recall (ROCF) (Table 2). Eighty percent of participants demonstrated a significant cognitive deficit, defined as having at least one cognitive test score that was 1.5 or more SD units below published normative data for each cognitive measure [15, 17–22].

Adjudication

Within the sample of middle-aged breast cancer survivors who underwent the cognitive assessment 1–5 years following adjuvant chemotherapy, thirty (50%) were adjudicated to be cognitively normal, twenty-six (43%) met NIA/AA criteria for MCI, 2% had dementia, and 5% could not be classified using the available data. Of those meeting criteria for MCI, 62% (16 patients) had amnestic MCI and 38% (10 patients) had non-amnestic MCI. Those with MCI had a median age of 54 with 73% between 50 and 59 years of age. Most were peri/post-menopausal (92%) and were 12–36 months post-chemotherapy (69%).

Discussion

The purpose of this study was to apply the well-established and accepted NIA/AA criteria for MCI in chemotherapy-treated breast cancer survivors with subjective cognitive symptoms as demonstrated by a FACT-COG PCI sub-score <63. In our 60 patient samples, 43% met criteria for MCI (Table 1). The average prevalence of MCI in major population based studies is 19% among patients 65 years and older [29].

To date, various studies of cognitive dysfunction among cancer survivors have used differing definitions of impairment (Table 3). Ahles et al. described long term cognitive impairment (minimum 5 years post diagnosis) in survivors of breast cancer or lymphoma treated with chemotherapy [2]. Cognitive impairment was defined as scoring in the lower quartile of their sample, equivalent to between 1 and 2 standard deviations below the mean, in at least 4 domains. Using this definition, they reported cognitive impairment in 39% of participants treated with chemotherapy as compared to 14% of those treated with local therapy only.

Wieneke and Dienst described cognitive impairment in breast cancer patients treated with chemotherapy within the preceding year [7]. Cognitive impairment was defined as mild: scoring greater than 1 standard deviation below the normative published mean on more than two tests, or moderate: scoring greater than 2 standard deviations below the normative published mean on at least one test. They reported moderate cognitive impairment in 75% of participants. Not surprisingly, by using various definitions of cognitive impairment assessed at different time intervals following completion of chemotherapy, estimates of impairment from retrospective studies have varied from 17 to 75% among breast cancer survivors [3,5,7,30–32].

Studies of change in cognitive function over time have been equally diverse. Wefel et al. conducted a prospective, longitudinal study of cognitive dysfunction in breast cancer patients receiving adjuvant chemotherapy [33]. Participants were administered a battery of neuropsychological tests that evaluated 7 cognitive domains at three points in time (before chemotherapy, six months after, 18 months after). Acquired cognitive impairment was defined as worsening in cognitive function, following treatment, of ≤ −1.5 SD units for more than 1 test or ≤ −2 for a single test. Using this definition, 61% of participants had a decline in 6 months post-treatment and, of these, 50% had not recovered 1 year after treatment. In another prospective, longitudinal study, Bender et al. compared three groups of breast cancer patients: chemotherapy treatment only, chemotherapy with tamoxifen, and local treatment only [34]. Cognitive functioning was assessed prior to chemotherapy, one week and one year after completion. Cognitive impairment was defined as a significant within group decline, or mean group performance significantly worse than another group on neuropsychological measures. Patients treated with chemotherapy had significantly worse performance on tests of verbal and visual memory test performance than the no treatment control group. Ganz et al. conducted a prospective, longitudinal, cohort study of 189 early-stage, post treatment (chemotherapy +/radiation) breast cancer patients to examine the association between subjective cognitive complaints and objective neuropsychological test performance [35]. Twenty three percent of patients reported memory symptoms and 19% reported symptoms of executive dysfunction that were associated with memory specific neuropsychological test performance and depressive symptoms.

Support for an effort to standardize the definition of cognitive impairment in cancer patients is growing. In 2003, a multidisciplinary workshop on the topic of chemotherapy related cognitive dysfunction called for interdisciplinary treatment and prevention studies of this under-recognized problem [36]. The workshop emphasized the importance of standard criteria to design large-scale clinical studies and identify sensitive neuropsychological tests. In 2007, Hurria, Somio, and Ahles proposed renaming “chemo-brain” as “cancer-or cancer-therapy-associated cognitive change,” but no specific criteria were put forth [37]. In an editorial in the Journal of the National Cancer Institute, Hede concluded that “chemo-brain is real but may need a new name” [38]. In response, we propose the term cancer-related Mild Cognitive Impairment (cMCI) to refer to those patients with a history of cancer and cancer treatment who also meet the NIA/AA criteria for MCI. A similar approach has been taken by the American Heart and Stroke Associations in their adoption of the term Vascular Cognitive Impairment (VCI) to refer to mild cognitive impairment that is cerebrovascular in origin [39, 40].

Implementation of standardized nomenclature will provide researchers with a common language to support the study of cancer and cancer treatment-related MCI and clinical, imaging, and genetic characteristics that might better predict cognitive decline. For example, in the general non-cancer population, prognostic factors most associated with progression of MCI to AD include the amnestic form of MCI [41], apolipoprotein ε4 carrier status, hippocampal or medial temporal lobe atrophy on MRI, temporoparietal hypometabolism/hypoperfusion on PET or SPECT imaging, evidence of Aβ deposition (low CSF Aβ42, positive PET imaging), and markers of tau accumulation (CSF tau/phosphorylated-tau) [8,42]. Combined with clinical criteria, these factors can predict, with various levels of certainty, the likelihood of progression from MCI to AD. Further research on whether similar factors are involved with the progression of cMCI to more advanced stages of cognitive dysfunction, including dementia, as well as longitudinal studies on the natural history of cMCI, are needed.

Strengths of this study include the prospective assessment of cognitive function in a well-defined cohort of breast cancer survivors, use of a validated neurocognitive test battery that assessed multiple cognitive domains, a high degree of participant adherence and retention, and the inclusion of both academic and community-based participating sites. The study has several limitations. It is retrospective in nature. Functional independence, one of the NIA/AA criteria for MCI was only indirectly evaluated using the FACIT-Fatigue rather than a thorough assessment of independent activities of daily living. Additionally, MCI criteria were originally developed to characterize syndromes associated with neurodegenerative disease, particularly Alzheimer's disease. The utility of applying these criteria to acute and chronic cognitive dysfunction resulting from cancer and its treatments is unknown.

Conclusion

In our population of breast cancer patients, 1–5 years following adjuvant chemotherapy, 43% met the NIA/AA criteria for MCI. Herein, we propose use of the term cancer-related Mild Cognitive Impairment (cMCI) to refer to those with a history of cancer who meet NIA/AA MCI criteria. Further longitudinal studies are needed to establish the validity and reliability of this diagnostic nosology and to identify prognostic factors associated with the progression of cMCI.

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Table 1

Patient Characteristics

	Overall	No MCI	MCI
Characteristic	# (%)	# (%)	# (%)
Total	60 (100)	34 (100)	26 (100)
Age			
Median (range)	55 (39–79)	55 (39–79)	54 (41–76)
Age ≥ 50	42 (70)	23 (68)	19 (73)
Age ≥ 60	23 (38)	14 (41)	9 (35)
BMI			
Median (range)	30.0 (20.0–46.9)	29.9 (22.0–46.9)	30.3 (20.0–43.7)
Underweight-Normal (< 25)	7 (12)	4 (12)	3 (12)
Overweight [25 – 30)	24 (40)	15 (44)	9 (35)
Obese [30+)	29 (48)	15 (44)	14 (54)
Menopause			
Pre	3 (5)	1 (3)	2 (8)
Peri/Post	57 (95)	33 (97)	24 (92)
Months since Chemotherapy			
12–36	40 (67)	22 (65)	18 (69)
36–60	20 (33)	12 (35)	8 (31)
Race/Ethnicity			
Black	5 (8)	1 (3)	4 (15)
White	54 (90)	33 (97)	21 (81)
Multiple	1 (2)	0 (0)	1 (4)
ECOG			
0	40 (67)	22 (65)	18 (69)
1	19 (32)	12 (35)	7 (27)
2	1 (2)	0 (0)	1 (4)
Health Insurance			
Private	49 (82)	28 (82)	21 (81)
Medicare	16 (27)	8 (24)	8 (31)
Medicaid	2 (3)	1 (3)	1 (4)
None	2 (3)	2 (6)	0 (0)
Marital Status			
Single	3 (5)	2 (6)	1 (4)
Married	43 (73)	26 (79)	17 (65)
Divorced/Widowed	13 (22)	5 (15)	8 (31)
Unknown	1 (--)	1 (--)	0 (--)
Education			

	Overall	No MCI	MCI
≤ High School	11 (19)	6 (18)	5 (20)
Some College	30 (51)	14 (41)	16 (64)
≥ College	18 (31)	14 (41)	4 (16)
Unknown	1 (--)	0 (--)	1 (--)
FACT-Cog			
≤ 20	23 (38)	12 (35)	11 (42)
21–30	15 (25)	10 (29)	5 (19)
31–40	14 (23)	7 (21)	7 (27)
41–50	7 (12)	4 (12)	3 (12)
≥ 51	1 (2)	1 (3)	0 (0)

Table 2

Baseline means, standard deviations, and ranges of cognitive test scores compared to normative data for each cognitive measure

Measure	Mean (SD)	Range (min–max)
HVLT-R Total	−0.68 (1.44)	−3.91 – 1.60
HVLT-R Delayed Recall	−0.62 (1.46)	−5.46 – 1.30
HVLT-R (% saved)	−0.39 (1.60)	−7.47 – 2.53
HVLT-R Discrimination	−0.22 (1.28)	−5.49 – 0.96
COWA	−0.51 (0.94)	−2.46 – 1.16
ROCF-Copy	−0.35 (1.29)	−4.90 – 2.24
ROCF-Immediate Recall	0.34 (0.92)	−1.85 – 1.79
ROCF-Delayed Recall	0.42 (0.93)	−1.60 – 1.94
Digit Span-Total	−0.02 (0.93)	−1.67 – 2.33
Trail Making Test A	−0.05 (1.38)	−4.65 – 1.79
Trail Making Test B	−0.90 (2.72)	−13.89 – 1.65
Groove Peg Dominant hand	−2.37 (2.64)	−12.09 – 1.25
Groove Peg Non-Dominant hand	−1.64 (2.20)	−12.46 – 3.29

Table 3

Review of breast cancer adjuvant and neoadjuvant chemotherapy literature

Reference	Study Type	n	Relationship to Treatment Time	Definition of Cognitive Impairment	Cognitive Domains Assessed	NP Tests Used	Self-Report QOL Measures	Outcomes
Ahles & Saykin, 20022	Cross-Sectional, two-group comparison	35	≥5 yrs post treatment (mean 9 yrs)	Score in the lower quartile on ≥ 4 domains	Attention, verbal learning, verbal memory; and psychomotor, spatial, and verbal abilities	WAIS-III[i], WRAT3[ii], BNT[iii], COWA[iv], CVLT[¶],WMS-R[#], TMT-A&B[v], Finger tapping, thumb finger sequencing, CPT[vi]	Squire Memory Self-Rating Questionnaire, CES-D[vii], STAI[viii], FSI[¶¶]	39% of chemo group impaired *vs* 14% in local rx group (<.01)
Bender et al., 200631	Prospective, three-group comparative study	34	Pre-chemo, ≤ 1 week post chemo, 1 year post chemo	NP testing score worse than another group (chemo *v* chemo + tamoxifen *v* local rx) (p<.05) or within-group decline, over time, on NP measures (p<.05)	Attention, executive function, general intelligence, learning, memory, mental flexibility, psychomotor speed, Visuo-constructional ability	Rey Auditory Verbal Learning Test, 4WSSTM[##], RCFT[***], WAIS[†††], TMT-A&B, GP[‡‡‡]	BDI[§§§], POMS[¶¶¶], PAOF[###]	• Chemo +/− tamoxifen: impaired verbal memory at 1 year • Chemo + tamoxifen: declined on visual, verbal, and working memory • Chemo alone: declined on verbal memory
Brezden et al., 20003	Cross-sectional, three-group comparative study	71	Currently receiving chemo ≥8 weeks or ≥1 year post chemo prior (median 25 months)	Worse NP test performance (domain specific and overall) compared to healthy controls (p<.05) and impairment classified according to HSCS [****](normal, borderline, abnormal and mild, moderate, severe)	Attention/ concentration, language, memory, self-regulation and planning; and spatial and visual-motor abilities	HSCS[****]	POMS[¶¶¶]	• Overall cognitive function significantly worse in current chemo group *vs* control (p=.009) • Moderate or severe cognitive impairment higher in both chemo groups *v* control (p<.002) • Impaired memory and language domains in current chemo v control (P=.024 and P=.033) • Impaired language and visual-motor skills in 1 year post-chemo v control (P=.047 and P = .024)
Donovan et al., 200528	Cross-sectional, between subjects	60	≥6 months after chemo completion	Test performance ≥ 2SDs below relevant published norms	Attention, complex cognition, episodic memory, language, motor skills, overall intellectual ability	COWA, CVLT, Finger Oscillation Test, NART[‡‡‡‡], TMT[v], WAIS-III, WMS-III[§§§§]	CES-D[vii], FSI[¶¶], MAQ[¶¶¶¶]	No significant (p<.05) difference in cognitive functioning between chemo and non-chemo groups

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Reference	Study Type	n	Relationship to Treatment Time	Definition of Cognitive Impairment	Cognitive Domains Assessed	NP Tests Used	Self-Report QOL Measures	Outcomes
Hurria et al., 200625	Prospective longitudinal	n=28	Pre-chemo, 6 months post chemo	NP performance ≥ 2SD below normative values on ≥ 2 tests and decline in cognitive functioning defined as decrease of ≥ 1 SD in ≥ 2 tests across ≥ 2 NP domains	Attention, verbal memory, visual memory; and verbal, spatial, psychomotor, and executive functions	BNT, COWA, HVLT-R ####, RCFT ***, Stroop Task, TMT-A&B[v], WAIS-III, WRAT3	Carlson Comorbidity Index, FACT-B *****, Katz ADL scale, KPS †††††, MMSE‡‡‡‡‡, Geriatric Depression Scale	−29% impaired at 6 months *v* 11% at pre-chemo
Jenkins et al., 200629	Prospective longitudinal	85	1, 12, and 18 months post chemo	Worse (p<.05) NP performance compared to non-chemo rx group or significant, within-group, decline from baseline (p<.05)	Executive function, processing speed, verbal memory, visual memory, working memory	A letter cancellation task, NART‡‡‡‡, RCFT, AVLT, Stroop Task, WMS-III	• Broad bent Cognitive Failures Questionnaire, FACT-B, FACT-ES §§§§§, FACT-F ¶¶¶¶¶, GHQ12######	No significant impairment in chemo rx group controlling for age/IQ
Schagen et al; 19994	Cross-Sectional Retro spective, two-group comparison	39	≥ 6 months post-chemo	≥ 2SD below mean of non-chemo rx group on ≥ 3 NP tests	Attention/ concentration, memory, mental flexibility, processing speed; and motor, verbal and visuo-onstructional functions	Dutch adult reading test, Fepsy finger tapping, Rey auditory verbal learning test, WAIS, WMS-R; and visual reaction, visual searching and binary choice tasks	EORTC QLQ ******, Hopkins Symptom Checklist-25, individual interviews	28% chemo group impaired *v* 12% of local rx group Chemo group significantly worse concentration (31% *vs.* 6%) and memory (21% *vs.* 3%) *v* local rx group
Tchen et al., 20035	Cross-sectional, two-group comparison	100	≥ 3 chemo cycles	HSCS scores used to identify performance as normal, borderline, mild, moderate or severe dysfunction	Attention/ concentration, language, psychomotor speed, self-regulation and planning, spatial, verbal memory, visual-motor ability	CPT, HSCS, TMT	FACT-ES, FACT-F, FACT-G †††††	Moderate or severe impairment in 16% of chemo group *v* 4% of controls (P=.008)
Wefel et al., 200430	Prospective longitudinal	n=18	Pre-chemo, 3 weeks post chemo, 1 year post chemo	Baseline impairment : z score ≤ −1.5 for ≥ 1 test and/or z scores ≤ − 2.0 for the results of a single test and significant (p<.01) within-group decline over time	Attention, learning, memory, processing speed; and executive, motor and visuospatial functions	Booklet Category Test, GP, NSVRT‡‡‡‡‡‡, TMT-A&B, VSRT§§§§§§, WAIS-R	FACT-B, MMPI######	33% impaired at baseline, 61% at 3 weeks (half remained impaired at 1 year)
Wieneke & Dienst, 19957	Cross-Sectional	28	Chemo within past 12 months, discontinued ≥ 2 weeks prior to testing	Compared scores to published norms. Mildly impaired: <1SD on ≥ 2NP tests; moderately impaired: criteria for mild + <2SD on ≥ 1NP test and clinical deterioration: ≥ 1SD decline from estimated baseline.	Abstract-concept visualization, attention/ concentration, language and verbal fluency, memory, mental flexibility, motor function, processing speed, visuospatial ability	COWA, CVLT, GP, NART-R, PASAT¶¶¶¶¶¶, RCFT, TMT A&B, WAIS-R	BDI	75% moderately impaired; clinically significant deterioration in all domains except abstract reasoning and verbal fluency

1 Weschler Adult Intelligence Scale- Revised III

1 Wide Range Achievement Test-3

1 Boston Naming Test

1 Controlled Oral Word Association Test

¶ California Verbal Learning Test

Weschler Memory Test Revised

1 Trail Making Tests A&B

1 Continuous Performance Test

1 The Center for Epidemiologic Study-Depression

1 Spielberger State-Trait Anxiety Inventory

¶¶ Fatigue Symptom Inventory

Four Word Short Memory Test

*** Rey Complex Figure Test

††† Weschler Adult Intelligence Scale

‡‡ Grooved Pegboard

§§§ Beck Depression Inventory

¶¶¶ Profile of Mood States

Patient's Assessment of Own Functioning Inventory

**** High Sensitivity Cognitive Screen

‡‡‡ National Adult Reading Test

§§§§ Weschler Memory Scale –III

¶¶¶¶ Multiple Abilities Questionnaire

Hopkins Verbal Learning Test-Revised

***** Functional Assessment of Cancer Therapy-Breast

††††† Karnofsky Performance Status

‡‡‡‡ Mini Mental Status Examination

§§§§§ Functional Assessment of Cancer Symptoms- Endocrine Symptoms

¶¶¶¶¶ Functional Assessment of Cancer Treatment-Fatigue

General Health Questionnaire 12

******* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

†††††† Functional Assessment of Cancer Treatment-General

‡‡‡‡‡ Nonverbal Selective Reasoning Test

§§§§§§ Verbal Selective Reminding Test

‖‖‖‖‖‖ Minnesota Multiphasic Personality Inventory

¶¶¶¶¶¶ Paced Auditory Serial Addition Test