Published in final edited form as:
Psychooncology. 2013 April ; 22(4): 862–868. doi:10.1002/pon.3086.

Cognitive Features Ten or More Years After Successful Breast Cancer Survival: Comparisons Across Types of Cancer Interventions

Christopher M. Nguyen[a,b], **Torricia H. Yamada**[c], **Leigh J. Beglinger**[d], **Joseph E. Cavanaugh**[e], **Natalie L. Denburg**[a], and **Susan K. Schultz**[d,*]

[a]Department of Neurology, Division of Behavioral Neurology and Cognitive Neuroscience, University of Iowa College of Medicine

[b]Counseling Psychology Program, Department of Psychological and Quantitative Foundations, University of Iowa College of Education

[c]Department of Psychology, Minneapolis VA Health Care System

[d]Department of Psychiatry, University of Iowa Carver College of Medicine

[e]Department of Biostatistics, University of Iowa College of Public Health

Abstract

The present study examined the long-term cognitive implications of cancer treatment among breast cancer survivors aged 65 years and older. Fifty-seven women survivors were compared to 30 healthy older female adult comparisons, matched in terms of age and education, with no history of cancer. Cancer survivors were also compared based on treatment intervention, involving chemotherapy ($n = 27$) versus local therapy through surgery and radiation ($n = 30$). As a group, the breast cancer survivors scored lower on measures of general cognitive function, working memory, psychomotor speed, and executive function, when compared to the normal comparisons. Among the cancer survivors, those who received local therapy scored lower than the other survivors and normal comparisons on measures of verbal learning, visual perception and construction, as well as visual attention and short-term retention. Our findings suggest that cognitive outcomes may involve more age-related deficits among older cancer survivors compared to matched healthy subjects.

Keywords

breast cancer; chemotherapy; cognition; neuropsychological assessment

According to the American Cancer Society there are almost two and a half million survivors of breast cancer and the median age at the time of diagnosis is 61 years. As the number of breast cancer survivors increase due to expanded treatment options, such as chemotherapy, the impact of such treatments on cognitive function becomes an increasing concern. For older breast cancer survivors successfully treated after diagnosis, there may remain residual concerns regarding whether exposure to cancer treatments may have latent effects on cognitive function as these individuals approach late-life. Neuropsychological evaluations on effects of treatments for all forms of cancer in adults have shown deleterious effects on

*Correspondence author. Address: Department of Psychiatry, Carver College of Medicine, University of Iowa Hospitals and Clinics, 500 Newton Road, Iowa City, IA 52242-1053, United States. Tel.: +1 319 335 6956; fax: +1 319 353 3003. susan-schultz@uiowa.edu (S.K. Schultz).

cognitive functioning that tend to persist in longitudinal follow-up (e.g., [1]). Other reviews featuring breast cancer patients have also suggested adverse effects of chemotherapy on cognition [2, 3, 4, 5, 6].

The possible neuropsychological side effects of these treatments may include difficulty concentrating, impaired memory, difficulty organizing information, processing speed, and decreased motor skills, and language problems. For example, a meta-analysis of 30 studies, encompassing 29 eligible samples across cancer groups (838 adults) by Anderson-Hanley *et al.* [7] indicated that patients who underwent chemotherapy showed the greatest changes in executive function and verbal memory when compared with matched comparisons. Furthermore, the analysis indicated that cancer patients consistently showed impairments in domains of executive functioning, verbal memory, and motor functioning compared to published normative data. In another meta-analysis, Falleti *et al.* [3] reported that breast cancer patients who received chemotherapy demonstrated decline in several cognitive domains (with small to medium effect sizes), including motor function, memory, executive functioning, and attention. A last meta-analysis [6], also with breast cancer participants, evaluated seven studies involving more than 300 participants and determined that breast cancer patients treated with chemotherapy displayed decline in language, spatial ability, and short-term memory.

There has been a variety of methodologies utilized to examine the possible deleterious effects on cognition in breast cancer patients. For example, some studies have compared breast cancer patients who have received chemotherapy to those who have received other forms of treatment and healthy matched comparisons (e.g., [8, 9]). Other studies have compared breast cancer patients based on chemotherapy dose, such as standard-dose versus higher doses of chemotherapy (e.g., [10, 11]). Many of these studies have been longitudinal (e.g., [9, 12, 13, 14, 15]), but some have been retrospective (e.g., [1, 16, 17]).

Two recent studies [13, 19] have specifically compared breast cancer patients who have received chemotherapy to breast cancer patients who have not received chemotherapy (e.g., local or radiotherapy only), and healthy controls. A study conducted in Canada [13] compared four groups (chemotherapy group, control group for chemotherapy group, radiotherapy group, and control group for radiotherapy group) of women prior to the start of chemotherapy, right after chemotherapy, and at a three-month follow-up. Each participant completed a neuropsychological battery and self-report questionnaires. Results across the three time points were mixed with breast cancer groups performing both better and worse compared to each other and their respective healthy comparison group. For example, both cancer groups demonstrated a decline in verbal memory between the first two time points, whereas nonverbal memory improved. Between the last two time points, participants demonstrated improvement on most cognitive measures.

A second study from the United Kingdom [18] sought to compare breast cancer patients being treated with chemotherapy, breast cancer patients being treated with radiotherapy, and a healthy control group at baseline, one month post-chemotherapy and 12 months post-chemotherapy. Results indicated that 22% of chemotherapy patients, 26% of radiotherapy patients, and 18% of healthy controls showed reliable decline on most neuropsychological measures. There were significant differences between the radiotherapy and control group on measures of memory and attention with the control group performing better.

While past research has established that a cohort of breast cancer patients frequently experience short-term cognitive deficits in the initial months and years following cancer treated with chemotherapy, the research has been variable in both the cognitive domain affected and severity. Furthermore, comparatively little has been done to systematically

assess the growing cohort of long-term aging survivors who may be disease-free for several decades after treatment. Specifically, it would be useful to understand whether cancer survivors are at greater risk for increased age-related brain changes or dementia secondary to cancer treatment. Although there have been longitudinal studies that have followed cancer survivors after treatment, very little has been done to examine the role of cognitive functioning in older breast cancer patients who are more than a decade post-chemotherapy. The present research attempts to assess long-term survivors over age 65 to determine whether any sustained cognitive liability is incurred from exposure to cancers treatments.

The primary goal of the present study was to determine whether a history of chemotherapy would be associated with cognitive deficits in excess of those observed in demographically matched healthy comparison women. Previous investigations from our laboratory have indicated that breast cancer patients, more than a decade post-chemotherapy, demonstrated significant differences and performed worse in the domains of attention, working memory, psychomotor speed, and aspects of executive functioning when compared to matched healthy community-dwelling older adults [17]. However, given that suffering from cancer may have independent effects beyond the impact of chemotherapy, it is also important to examine women with a history of breast cancer but treated with local therapy (as opposed to chemotherapy). Therefore, a second group of cancer survivors were recruited and comprised of women treated with surgical removal and local radiation for breast cancer. We hypothesized that a history of cancer would be associated with greater cognitive deficits when compared to an age-, education, and intellect-matched sample of healthy, community-dwelling older adults. Also, women who were exposed to chemotherapy would endorse greater cognitive deficits when compared to women who had been treated with surgical removal and local radiation.

Methods

Participants

Fifty-seven breast cancer survivors (hereafter referred to as BCS) participated in the study. The BCS were recruited in collaboration with the Iowa Cancer Registry, a statewide registry of cancer patients begun in 1973. Notably, the registry collects information on diagnosis of all cancers in the State of Iowa, including tissue type, stage of cancer and type of treatment. The registry undergoes continuous updates so the recurrence of breast cancer or other cancers would be noted. Enrollment criteria specified that the participants were women over the age of 65 years, at least 50 years of age at the time of cancer diagnosis, and at least 10 years post-cancer treatment without recurrence. Participants for this study were diagnosed and treated for early malignant breast cancer Stage I through Stage IIIA without evidence of metastasis. Participants were excluded if there had been a recurrence of any kind of cancer in the 10–15 year period since initial diagnosis, excluding basal cell or relatively benign skin lesions. Participants were also excluded if they possessed a central nervous system (CNS) disorder, such as multiple sclerosis, Parkinson’s disease, closed head trauma with an extended loss of consciousness, or other CNS lesion. All breast cancer survivors were free of currently active and unstable metabolic, psychiatric, and cardiovascular diseases, including cerebrovascular events and substance abuse.

The participants in the chemotherapy group had received a standard multi-agent chemotherapy regimen involving cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or an anthracycline (doxorubicin) following their initial surgical excision of the cancer. Participants in the local-therapy group had all received surgery and/or received local radiation to the affected breast.

Non-cancer comparison participants were identified from an existing database. These "comparisons" (hereafter referred to as NC) were previously recruited in the community for an ongoing study examining the effects of aging on decision-making behavior. As such, only healthy, community-dwelling adults were included. Participants met inclusionary criteria if they were free of neurological and psychiatric illness.

Measures

Each participant completed a comprehensive neuropsychological battery of approximately 3-hours duration consisting of standardized clinical instruments designed to assess a broad range of cognitive skills and emotional functioning, including current and premorbid intellect, mental status, attention and working memory, psychomotor speed, language, visuospatial skills, memory, executive functioning, mood, and medical comorbidity. Table 1 display individual names of neuropsychological measures by cognitive domain.

Procedure

Participants signed a written informed consent document approved by the University of Iowa Institutional Review Board and were financially compensated for their involvement.

Statistical Analyses

Preliminary analysis examined data for the presence of outliers and the appropriateness of assumptions of normality, linearity, and homogeneity of variances. A one-way analysis of variance (ANOVA) was computed using the cognitive measures as dependent variables and the participant groups (i.e., chemotherapy, local-therapy, non-cancer) as independent variables. To control for inflation of the experiment-wise type 1 error, the Hochberg procedure [33] was used to account for multiple comparisons. The next set of analyses explored group differences on individual neuropsychological tests, using a series of one-way analyses of covariance (ANCOVA) with age, education, and medical comorbidity as the covariates and each test score as the dependent variable. The ANCOVAs were applied to measures displaying significant group differences after the Hochberg procedure.

Results

The final sample was comprised of 87 subjects. The chemotherapy-exposed group included 27 participants, with a mean age of 72.0 years (SD = 4.9; range [66–85]), a mean education of 14.6 years (SD = 2.8; range [11–20]), a WASI Full-Scale IQ of 114.5 (SD = 12.11), and a WRAT-III reading raw score of 48.1 (SD = 4.7). The local therapy group included 30 participants, with a mean age of 76.7 years (SD = 5.4; range [69–89]), mean education of 14.2 years (SD = 2.1; range [11–19]), a WASI Full-Scale IQ of 111.7 (SD = 14.9), and a WRAT-III reading raw score of 48.7 (SD = 4.1).

The non-cancer comparison group had a mean age of 72.6 years (SD = 5.5; range [65–85]), a mean education of 14.3 years (SD = 2.2; range [11–18]), a WASI Full-Scale IQ of 112.9 (SD = 9.9), and a WRAT-III reading raw score of 50.2 (SD = 5.0). We observed significant differences among the three participants groups in terms of age, such that the surgery group were significantly older than both the chemotherapy and NCs [$F(2, 86) = 7.07$, $p = .001$]. The three groups did not significantly differ in terms of education, overall premorbid and current intelligence, self-reported mood, or medical comorbidity. Demographic variables are presented in Table 2.

Table 2 displays the results of between-subjects effects from ANOVA analysis. After applying the Hochberg procedure, we observed significant differences among the three participant groups on the following neuropsychological measures: MMSE [$F(2, 86) = 10.72$,

$p < .001$]; Letter-Number Sequencing [$F(2, 86) = 10.58$, $p < .001$]; WCST categories [$F(2, 86) = 14.46$, $p < .001$]; Trail Making A [$F(2, 86) = 8.75$, $p < .001$]. Tukey post-hoc comparisons of the three groups indicated that the NC group outperformed the BCS in the aforementioned measures of mental status, attention and working memory, psychomotor speed, and executive function.

In the domain of verbal learning and visual perception, there were significant differences among the three participant groups on the RAVLT total recall [$F(2, 86) = 6.42$, $p = .003$] and Rey-O Copy [$F(2, 86) = 18.68$, $p < .001$], such that local-therapy group underperformed in comparison to the chemotherapy and NC groups. Group differences were also observed in the aspects of visual attention and short-term retention. Specifically, there were group differences in BVRT [$F(2, 86) = 5.92$, $p = .004$], such that local-therapy group performed worse in comparison to the NC group. Results of the ANOVA post-hoc analyses are presented in Table 3.

The univariate ANCOVAs presented in Table 4 indicate significant differences between the groups that are consistent with results from the analysis of variance, with the exception of performances on the BVRT and RAVLT. For performance on the BVRT, an ANCOVA revealed a significant main effect, [$F(2,86)) = 6.747$; $p = .002$)], with post-hoc analysis using Tukey's HSD indicated that the local-therapy group underperformed in comparison to both the chemotherapy ($p = .04$) and NC group ($p = .001$).

For performances on the RAVLT, an ANCOVA [$F(2, 86) = 3.081$, $p = .052$] revealed a change in the main effects when compared with results of the ANOVA [$F(2, 86) = 6.42$, $p = .003$]. However, post-hoc analysis revealed similar findings, such that the local-therapy group underperformed in comparison to the chemotherapy ($p = .029$) and normal control ($p = .044$) groups. Results of the ANCOVA post-hoc analyses are presented in Table 2.

Overall, results from the univariate ANCOVAs suggested that even after controlling for age, education, and medical cormorbidity, the BCS group scored lower on the MMSE, Letter-Number Sequencing, Trail Making A, and WCST. In addition, when cancer survivors were compared based on whether they received chemotherapy or not, the local-therapy group scored lower than the chemotherapy-exposed and non-cancer group on the RAVLT and BVRT.

Discussion

The aim of this study was to evaluate the effects of chemotherapy on cognition in long-term survivors of breast cancer. We further assessed for differential effects among various treatment modalities by comparing chemotherapy-exposed to non-chemotherapy-exposed survivors (i.e., local-therapy). We hypothesized that a history of cancer would be associated with greater cognitive deficits when compared to a matched sample of healthy, community-dwelling older adults, and that chemotherapy survivors would endorse greater cognitive deficits when compared to local therapy survivors.

Our findings confirm those of previous studies examining the effects of cancer on cognitive outcomes. Specifically, we observed evidence of lower general mental status (MMSE), reduced performance in working memory function (Letter Number Sequencing), and weaker executive functioning (Wisconsin Card Sorting Task). The NC group outperformed both cancer treatment groups in the aforementioned measures. These findings are consistent with past studies, suggesting that patients exposed to chemotherapy showed a decline in cognitive performance compared with healthy comparison subjects (e.g., [1, 7, 11, 12]).

Interestingly, cancer survivors who had not been exposed to chemotherapy scored lower than the other survivors and NCs on measures of verbal learning (RAVLT), visual perception (Rey figure), as well as visual attention and short-term retention (BVRT). Participants from the local-therapy group were significantly older than both the chemotherapy and non-cancer group, yet these difference persisted after controlling for age differences. Given that the tests involved included verbal learning and short-term retention, one might surmise that these individuals displayed cognitive changes in a pattern that is consistent with age-related cognitive changes, but perhaps at a slightly more accelerated pace due to the effects of surviving the cancer and local-therapy. That is, an accelerated normal aging process secondary to a vulnerable brain given a history of cancer and therapy is plausible.

It is not clear why the chemotherapy group did not show the verbal learning changes that were evident in the local-therapy cancer group. This was inconsistent with our expectation that chemotherapy would incur an additional vulnerability to the other deleterious effects of experiencing a cancer diagnosis and treatment. Unfortunately, the survivorship literature about the persistent effects of chemotherapy has been variable and, for example, the long-term effects of chemotherapy on cognition with survivors who received high-dose treatment, standard treatment, and no chemotherapy treatment (i.e., surgery and radiation therapy only) approximately five years post-treatment revealed no group differences [34]. In contrast, Ahles *et al.* [1] found that survivors treated with systemic chemotherapy scored significantly lower on tests of verbal memory and psychomotor functioning compared with those treated with local therapy only more than five years post-diagnosis.

For our present findings, subtle differences in general health, disease severity, or selection factors that were not discernable by our selection procedures (e.g., differences in the type of cancer treatment selection despite similar cancer staging), are likely factors that may play a role in survivorship differences that are undetectable. Additionally, the nature of combination chemotherapy treatment does not allow us to identify the individual effects of each specific chemotherapy regimens (i.e., cyclophosphamide versus anthracycline). However, variations in chemotherapy treatment have not been implicated to display differences in cognitive effects. In a study examining the long-term cognitive effects of adjuvant chemotherapy in older women diagnosed with breast cancer (n = 6,932), Raji *et al.* [35] found no significant association between types of chemotherapy agents (e.g., Anthracycline, CMF, Taxane, and others) and risk of dementia diagnoses.

There are some limitations to this study. A larger sample may have helped us better distinguish the neuropsychological patterns between subjects exposed to surgical treatment compared to chemotherapy treatment. Furthermore, group differences were not observed for mood in our sample but further exploration of other factors such as anxiety may have also helped distinguish the groups, although it is important to note that being ten years since diagnosis without recurrence, our participants were past the typical phase of cancer-related stress that is observed at the time of acute diagnosis and initial treatment. Despite being past the initial phase of treatment-related stress, it is possible that other psychosocial stressors may have been playing a role in the cognitive outcomes of this sample that we failed to detect in this sample. It is also possible that endocrine therapy and early menopause has the potential to affect the variance in cognition particularly in the chemotherapy-exposed group. However, in this group the mean duration since the initial diagnosis of cancer was 16.8 years (SD = 2.8; range 13.8–22.5 years). Consequently time elapsed between menopause and/or endocrine therapy (e.g., tamoxifen) and our assessment would have been for a substantial duration, as tamoxifen is utilized only for the first five years after cancer diagnosis. Approximately half our sample received tamoxifen and half did not and we did not find that its presence affected the neuropsychological measures in our study. Finally, limitations of

cross-sectional study design have been discussed by the International Cognition and Cancer Task Force [36]. Specifically, interpretations of results may be limited due to group differences among comparison groups (e.g., patients exposed to chemotherapy to those exposed to surgical removal and local radiation). Therefore, differences in neuropsychological outcomes may not necessarily reflect changes caused by chemotherapy.

These preliminary analyses of the effects of chemotherapy on long-term survivorship in breast cancer can provide a foundation for future studies. Specifically, these data may serve as a baseline as our study progresses to include longitudinal neuropsychological evaluations. As the number of long-term survivors continue to increase, efforts to better understand the implications of systemic interventions of cancer is necessary.

Acknowledgments

Preparation of this manuscript was supported by the National Institute of Health grant NCI R01CA122934; National Institute on Aging Career Development Award to Natalie L. Denburg (K01 AG022033); and by an Agency for Healthcare Research and Quality (AHRQ) Centers for Education and Research on Therapeutics cooperative agreement #5 U18HSO16094.

References

1. Ahles TA, Saykin AJ, Fustenberg CT, et al. Neuropsychologic impact of standard-dose chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol. 2002; 20:485–493. [PubMed: 11786578]
2. Bender CM, Paraska KK, Sereika SM, Ryan CM, Berga SL. Cognitive function and reproductive hormones in adjuvant therapy for breast cancer: A critical review. J Pain Symptom Manage. 2001; 21:407–424. [PubMed: 11369162]
3. Falleti MG, Sanfilippo A, Maruff P, Weih L, Philips KA. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: A meta-analysis of the current literature. Brain Cognition. 2005; 59:60–70.
4. Olin JJ. Cognitive function after systemic therapy for breast cancer. Oncology. 2001; 15:613–621. [PubMed: 11396356]
5. Reid-Arndt S. The potential for neuropsychology to inform functional outcomes research with breast cancer survivors. NeuroRehabilitation. 2006; 21:51–64. [PubMed: 16720938]
6. Stewart A, Bialajew C, Collins B, Parkinson M, Tomiak E. A meta- analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. Clin Neuropsychol. 2006; 20:76–89. [PubMed: 16410227]
7. Anderson-Hanley C, Sherman ML, Riggs R, Agocha VB, Compas BE. Neuropsychological effects of treatments for adults with cancer: A meta- analysis and review of the literature. J Int Neuropsychol Soc. 2003; 9:967–982. [PubMed: 14738279]
8. Bender CM, Sereika SM, Berga SL, et al. Cognitive impairment associated with adjuvant therapy in breast cancer. Psycho-Oncology. 2006; 15:422–430. [PubMed: 16097037]
9. Stewart A, Collins B, Mackenzie J, et al. The cognitive effects of adjuvant chemotherapy in early stage breast cancer: A prospective study. Psycho-Oncology. 2008; 17:122–130. [PubMed: 17518411]
10. Mehnert A, Scherwath A, Schirmer L, et al. The association between neuropsychological impairment, self-perceived cognitive deficits, fatigue and health-related quality of life in breast cancer survivors following standard adjuvant versus high-dose chemotherapy. Patient Educ Couns. 66:108–118. [PubMed: 17320337]
11. Schagen SB, Muller MJ, Boogerd W, et al. Late effects of adjuvant chemotherapy on cognitive function: A follow-up study in breast cancer patients. Ann Oncol. 2002; 13:1387–1397. [PubMed: 12196364]
12. Hurria A, Rosen C, Hudis C, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: A pilot prospective longitudinal study. J Am Geriatr Soc. 2006; 54:925–931. [PubMed: 16776787]

13. Quesnel C, Savard J, Ivers H. Cognitive impairments associated with breast cancer treatments: Results from a longitudinal study. Breast Cancer Res Tr. 2009; 116:113–123.
14. Reid-Arndt SA, Hsieh K, Perry MC. Neuropsychological functioning and quality of life during the first year after completing chemotherapy for breast cancer. Psycho-Oncology. 2010; 19 :535–544. [PubMed: 19472296]
15. Wefel JS, Saleeba AK, Buzdar AU, Meyers CA. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer. 2010; 116:3348–3356. [PubMed: 20564075]
16. Brezden CB, Phillips K, Abdolell M, Bunston R, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol. 2000; 18:2695–2701. [PubMed: 10894868]
17. Yamada TH, Denburg NL, Beglinger LJ, Schultz SK. Neuropsychological outcomes of older breast cancer survivors: Cognitive features ten or more years after chemotherapy. J Neuropsych Clin N. 2010; 22:48–54.
18. Jenkins V, Schilling V, Deutsch G, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Brit J Cancer. 2006; 94:828–834. [PubMed: 16523200]
19. Wechsler, D. The WASI: Wechsler Abbreviated Scale of Intelligence. San Antonio, Texas: Psychological Corp; 1999.
20. Wilkinson, GS. WRAT-3: Wide Range Achievement Test Administration Manual. 3. Wilmington, Delaware: Wide Range; 1993.
21. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
22. Wechsler, D. Wechsler Adult Intelligence Scale–III. San Antonio, Texas: Psychological Corp; 1997.
23. Spreen, O.; Strauss, E. A Compendium of Neuropsychological Tests. 2. New York, New York: Oxford University Press; 1998.
24. Benton, AL.; Hamsher, K. Multilingual Aphasia Examination. Iowa City, Iowa: AJA Associates; 1989.
25. Kaplan, EF.; Goodglass, H.; Weintraub, S. Boston Naming Test. Philadelphia, Pennsylvania: Lea & Febiger; 1983.
26. Rey A. L’examen psychologique dans les cas d’encephalopathie traumatique. Arch Psychologie. 1941; 28:286–340.
27. Benton, AL.; Sivan, AB.; Hamsher, K.; Varney, NR.; Spreen, O. Contributions to Neuropsychological Assessment: A Clinical Manual. 2. New York, New York: Oxford University Press; 1994.
28. Rey, A. L’examen Clinique en Psychologie. Paris, France: Presses Universitaires de France; 1964.
29. Benton AL. A visual retention test for clinical use. Arch Neuro Psychiatr. 1945; 54:212–216.
30. Heaton, RK.; Chelune, GJ.; Talley, JL.; Kay, GG.; Curtiss, G. Wisconsin Card Sorting Test manual: Revised and expanded. Odessa, FL: Psychological Assessment Resources; 1993.
31. Beck, AT.; Steer, RA.; Brown, G. Beck Depression Inventory–II: Manual. San Antonio, Texas: Psychological Corp; 1996.
32. Piccirillo JF, Costas I, Claybour P, et al. The measurement of comorbidity by cancer registries. J Registry Manage. 2003; 30:8–14.
33. Hochberg Y. A sharper Bonferroni procedure formultiple tests of significance. Biometrika. 1998; 75:800–802.
34. Scherwath A, Mehnert A, Schleimer B, et al. Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: evaluation of long-term treatment effects. Ann Oncol. 2006; 17:415–423. [PubMed: 16357023]
35. Raji MA, Tamborello LP, Kuo YF, et al. Risk of subsequent dementia diagnoses does not vary by types of adjuvant chemotherapy in older women with breast cancer. Med Oncol. 2009; 26:452–459. [PubMed: 19067255]

36. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011; 12:703–08. [PubMed: 21354373]

TABLE 1

Neuropsychological Measures by Cognitive Domain

Cognitive Domain	Neuropsychological Measures
Intelligence and Mental Status	Wechsler Abbreviated Scale of Intelligence (WASI; [19])
	Wide Range Achievement Test–III Reading subtest (WRAT-III; [20])
	Folstein Mini Mental State examination (MMSE; [21])
Attention and Working Memory	Digit Span, Letter-Number Sequencing, and Arithmetic subtests from the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III; [22])
Psychomotor Speed	Trail Making Test, Part A (Trail Making A; [23])
Language	Controlled Oral Word Association Test (COWAT; [24])
	Boston Naming Test (BNT; [25])
Visuospatial	Rey-Osterrieth Complex Figure Test-Copy Condition (Rey-O Copy; [26])
	Benton Facial Recognition Test (Benton Faces; [27])
Memory	Rey Auditory-Verbal Learning Test (RAVLT; [28])
	Rey-Osterrieth Complex Figure Test-Delay Condition (Rey-O Delay; [26])
	Benton Visual Retention Test-Revised (BVRT-R; [29])
Executive Functioning	Wisconsin Card Sorting Test (WCST; [30])
	Trail Making Test, Part B (Trail Making B; [23])
Mood	Beck Depression Inventory-II (BDI-II; [31])
Medical Comorbidity	Adult Comorbidity Evaluation-27 (ACE-27; [32])

TABLE 2

Between-Subjects Effects from ANOVA

Measure	Chemotherapy (n=27)	Local-therapy (n=30)	Non-Cancer (n=30)	F	P
Age (years)	72.0 (4.9)	76.7 (5.4)	72.6 (5.5)	7.07	.001*
Education (years)	14.6 (2.8)	14.2 (2.1)	14.3 (2.2)	.18	.838
Wechsler Abbreviated Scale of Intelligence					
Vocabulary	64.5 (7.8)	60.9 (8.2)	63.7 (6.9)	1.65	.198
Block Design	33.9 (12.3)	32.0 (13.4)	34.8 (11.9)	.14	.871
Similarities	36.8 (4.8)	35.8 (5.2)	36.6 (3.0)	.133	.893
Matrix Design	20.6 (6.5)	17.9 (7.1)	21.8 (6.8)	2.45	.093
Wide Range Achievement Test–III reading subtest	48.1 (4.7)	48.7 (4.1)	50.2 (5.0)	1.697	.191
Folstein Mini-Mental State Examination	28.0 (1.7)	27.5 (2.1)	29.4 (0.7)	10.72	.000*
Digit span total raw score	15.5 (3.4)	15.2 (3.2)	16.9 (4.4)	1.93	.151
Letter-Number Sequencing total raw score	9.1 (2.1)	8.7 (2.0)	11.0 (2.0)	10.58	.000*
Arithmetic total raw score	12.4 (2.8)	12.3 (3.8)	13.7 (3.2)	1.56	.216
Trail Making test					
A – time (s)	37.8 (8.9)	39.4 (12.2)	29.27 (8.7)	8.75	.000*
B – time (s)	97.0 (35.5)	100.3 (53.4)	72.4 (26.6)	4.28	.017
Controlled Oral Word Association Test	39.4 (15.1)	37.0 (9.8)	38.8 (11.1)	.31	.731
Boston Naming Test total raw score	57.0 (2.5)	52.8 (10.3)	56.1 (3.0)	3.37	.039
Rey-Osterrieth Complex Figure					
Total copy score	33.3 (2.0)	29.2 (2.9)	32.0 (2.9)	18.68	.000*
Total delay score	15.9 (5.1)	11.6 (6.0)	15.6 (5.6)	5.46	.006
Benton Faces total raw score	44.4 (3.4)	43.2 (3.6)	45.5 (3.8)	3.13	.049
Benton Visual Retention Test total error score	5.3 (2.2)	6.8 (2.3)	4.4 (2.8)	5.92	.004*
Rey Auditory-Verbal Learning Test total recall	48.6 (8.3)	41.8 (9.8)	49.4 (8.7)	6.42	.003*
Rey Auditory-Verbal Learning Test 30 minute delay	10.2 (2.6)	8.7 (3.4)	10.6 (2.3)	3.85	.025
IED Stage 5 errors	3.2 (4.2)	2.1 (1.5)	1.3 (1.0)	3.59	.032
Wisconsin Card Sorting Test					
Perseverative	12.5 (6.9)	12.8 (9.3)	16.6 (12.2)	1.452	.241

Measure	Chemotherapy (n=27)	Local-therapy (n=30)	Non-Cancer (n=30)	F	P
Errors	11.0 (5.7)	11.1 (7.7)	14.9 (11.0)	1.754	.180
Categories	2.9 (1.6)	2.8 (1.5)	5.0 (1.9)	14.46	.000 *
Beck Depression Inventory-II total raw score	5.7 (5.1)	6.4 (5.4)	4.0 (3.4)	1.99	.143
Adult Comorbidity Evaluation index	.96 (.66)	.97 (.56)	.84 (.69)	.242	.786

* Significant P-value after Hochberg correction for multiple comparisons.

TABLE 3

Tukey HSD Comparison from ANOVA and ANCOVA

Measure	Group (I)	Group (J)	ANOVA			ANCOVA		
			Mean Diff (I-J)	Std. Error	Sig.	Mean Diff (I-J)	Std. Error	Sig.
MMSE	Chemo	Local-therapy	.500	.428	.475	.270	.487	.581
		Non-Cancer	−1.367*	.428	.006	−1.458*	.511	.006
	Local-therapy	Chemo	−.500	.428	.475	−.270	.487	.581
		Non-Cancer	−1.867*	.416	.000	−1.727*	.525	.002
	Non-Cancer	Chemo	1.367*	.428	.006	1.727*	.525	.002
		Local-therapy	1.867*	.416	.000	1.458*	.511	.006
LN - Total raw score	Chemo	Local-therapy	.333	.549	.816	.180	.587	.760
		Non-Cancer	−1.926*	.535	.002	−1.882*	.611	.003
	Local-therapy	Chemo	−.333	.549	.816	−.180	.587	.760
		Non-Cancer	−2.259*	.535	.000	−2.062*	.635	.002
	Non-Cancer	Chemo	1.926*	.535	.002	2.062*	.635	.002
		Local-therapy	2.259*	.535	.000	1.882*	.611	.003
Trail A – time (s)	Chemo	Local-therapy	−1.619	2.672	.817	1.805	2.853	.529
		Non-Cancer	8.548*	2.672	.005	8.856*	2.995	.004
	Local-therapy	Chemo	1.619	2.672	.817	−1.805	2.853	.529
		Non-Cancer	10.167*	2.600	.001	7.051*	3.079	.025
	Non-Cancer	Chemo	−8.548*	2.672	.005	−7.051*	3.079	.025
		Local-therapy	−10.167*	2.600	.001	−8.856*	2.995	.004
Rey-O Copy	Chemo	Local-therapy	4.150*	.699	.000	3.584*	.670	.000
		Non-Cancer	1.317	.699	.063	.203	.703	.774
	Local-therapy	Chemo	−4.150*	.699	.000	−3.584*	.670	.000
		Non-Cancer	−2.833*	.681	.000	−3.382	.722	.000
	Non-Cancer	Chemo	−1.317	.699	.063	−.203	.703	.774
		Local-therapy	2.833*	.681	.000	3.382*	.722	.000

Measure	Group (I)	Group (J)	ANOVA			ANCOVA		
			Mean Diff (I-J)	Std. Error	Sig.	Mean Diff (I-J)	Std. Error	Sig.
BVRT - Total error score	Chemo	Local-therapy	−1.523	.697	.081	−1.446*	.704	.044
		Non-Cancer	.899	.682	.390	1.347	.719	.066
	Local-therapy	Chemo	1.523	.697	.081	1.446*	.704	.044
		Non-Cancer	2.423*	.710	.003	2.793*	.761	.001
	Non-Cancer	Chemo	−.899	.682	.390	−2.793*	.761	.001
		Local-therapy	−2.423	.710	.003	−1.347	.719	.066
RAVLT - Total recall	Chemo	Local-therapy	6.793*	2.380	.015	5.504*	2.473	.029
		Non-Cancer	−.807	2.380	.939	.026	2.596	.992
	Local-therapy	Chemo	−6.793*	2.380	.015	−5.504*	2.473	.029
		Non-Cancer	−7.600*	2.317	.004	−5.478*	2.669	.044
	Non-Cancer	Chemo	.807	2.380	.939	5.478*	2.669	.044
		Local-therapy	7.600*	2.317	.004	−.026	2.596	.992
WCST - Categories	Chemo	Local-therapy	.114	.500	.972	−.067	.481	.890
		Non-Cancer	−2.111*	.460	.000	−2.677*	.461	.000
	Local-therapy	Chemo	−.114	.500	.972	.067	.481	.890
		Non-Cancer	−2.225*	.488	.000	−2.610*	.507	.000
	Non-Cancer	Chemo	2.111*	.460	.000	2.610*	.507	.000
		Local-therapy	2.225*	.460	.000	2.677*	.461	.000

*The mean difference is significant at the 0.05 level.

TABLE 4

Between-Subjects Effects from ANOVA and ANCOVA

Measure	Chemotherapy (n=27)	Local-therapy (n=30)	Non-Cancer (n=30)	F	P	Sig. Main Effects
MMSE	28.0 (1.7)	27.5 (2.1)	29.4 (0.7)	10.72	.000	Non-Cancer > Chemo & Local-therapy
	27.9 (.34)	27.6 (.33)	29.3 (.40)	6.16	.003	Non-Cancer > Chemo & Local-therapy *
LN - Total raw score	9.1 (2.1)	8.7 (2.0)	11.0 (2.0)	10.58	.000	Non-Cancer > Chemo & Local-therapy
	9.0 (.40)	8.8 (.41)	10.9 (.47)	6.46	.003	Non-Cancer > Chemo & Local-therapy *
Trail A - Time (s)	37.8 (8.9)	39.4 (12.2)	29.3 (8.7)	8.75	.000	Non-Cancer < Chemo & Local-therapy
	39.2 (1.97)	37.4 2(1.9)	30.3 (2.3)	4.67	.013	Non-Cancer < Chemo & Local-therapy *
Rey-O - Total copy score	33.3 (2.0)	29.2 (2.9)	32.0 (2.9)	18.68	.000	Local-therapy < Chemo & Non-Cancer
	33.1 (.46)	29.5 (.45)	32.9 (.5)	17.09	.000	Local-therapy < Chemo & Non-Cancer *
BVRT - Total error score	5.3 (2.2)	6.8 (2.3)	4.4 (2.8)	5.92	.004	Local-therapy > Non-Cancer
	5.3 (.46)	6.76 (.51)	4.0 (.56)	6.75	.002	Local-therapy > Chemo & Non-Cancer *
RAVLT - Total recall	48.6 (8.3)	41.8 (9.8)	49.4 (8.7)	6.42	.003	Local-therapy < Chemo & Non-Cancer
	48.1(1.7)	42.6 (1.67)	48.1 (2.0)	3.08	.052	Local-therapy < Chemo & Non-Cancer *
WCST -Categories	2.9 (1.6)	2.8 (1.5)	5.0 (1.9)	14.46	.000	Non-Cancer > Chemo & Local-therapy
	2.9 (.31)	2.9 (.35)	5.5 (.35)	20.09	.000	Non-Cancer > Chemo & Local-therapy *

* Results of each analysis of covariance for the respective neuropsychological measure; the adjusted means were obtained and reported.