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A randomized trial of cognitive rehabilitation in cancer survivors: A preliminary study

M.M. Cherrier [a,d,*], K. Anderson [a], D. David [a], C. Higano [c], H. Gray [b,c,d], A. Church [a], S. Willis [a]

[a] University of Washington, Department of Psychiatry and Behavioral Sciences, Seattle, WA, USA
[b] University of Washington, Department of Obstetrics and Gynecology, Seattle, WA, USA
[c] University of Washington, Department of Medicine, Division of Oncology, Seattle, WA, USA
[d] Fred Hutchinson Cancer Research Center, USA

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ABSTRACT

Aims: The second most frequently reported post-treatment symptom in cancer survivors concerns about impaired cognition. Despite numerous studies demonstrating significant impairments in a portion of survivors, information on effective treatments remains an emerging area of research. This study examined the effectiveness of a group-based cognitive rehabilitation intervention in cancer survivors.
Main methods: This study was a randomized, controlled study of a 7-week cognitive rehabilitation intervention delivered in group format. Participants were evaluated with subjective symptom questionnaires and objective neurocognitive tests prior to and following treatment.
Key findings: Twenty-eight participants (mean age 58 years) with a median of 3 years (±6 years) post-primary/adjuvant treatment and various cancer sites (breast, bladder, prostate, colon, uterine) completed the study. Compared to baseline, the treatment group demonstrated improvements in symptoms of perceived cognitive impairments ($p < .01$), cognitive abilities ($p < .01$) and overall quality of life with regard to cognitive symptoms ($p < .01$) as measured by the FACT-Cog. The treatment group also improved on objective measures of attention ($p < .05$) and a trend toward improvement on verbal memory. Significant improvement was not observed on all cognitive tests.
Significance: A group based cognitive rehabilitation intervention in cancer survivors was effective for improving attention abilities and overall quality of life related to cognition. Results suggest that group based cognitive rehabilitation may be an effective intervention for treating cognitive dysfunction in cancer patients and should be further studied in a larger trial with an active control condition.

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Introduction

Millions of cancer survivors live with residual symptoms of impaired cognition severe enough to interfere with basic activities of daily living and work (Cavanna et al., 2011). Although some studies indicate persistent cognitive deficits in cancer survivors related to chemotherapy or use of tamoxifen (Debess et al., 2010; Koppelmans et al., 2012), findings in this regard are equivocal.(Du et al., 2010; Harrington et al., 2010; Pedersen et al., 2009) Despite numerous studies demonstrating significant cognitive impairments in a portion of survivors, research into effective treatments for cognitive difficulties is an emerging area of enquiry (Loiselle and Rockhill, 2009; Marín et al., 2009; Vardy, 2009; Wefel et al., 2010). Cognitive rehabilitation has been utilized successfully for many years in the context of brain injury programs (Sohlberg and Mateer, 2001). Cognitive rehabilitation and cognitive training have also been shown to be effective in helping children with cancer achieve school success (Butler et al., 2008) and more recently to improve cognition in older adults with mild cognitive impairment (MCI), multiple-sclerosis, schizophrenia and brain tumor patients (Gehring et al., 2010; Hassler et al., 2010; Haut et al., 2010; Mattioli et al., 2010; Poppelreuter et al., 2008; Pyun et al., 2009). In cancer survivors, cognitive behavioral treatment can be effective for improving memory and attention problems (Ferguson et al., 2007, 2012). In general, studies indicate some success for goal development as well as over learning or repeated practice approaches, as well as an indication that a deficit specific approach can be useful. See Rajeswaran for a comprehensive review (Rajeswaran, 2013).

In this preliminary study, we examined a randomized, controlled trial of a 7-week, group based cognitive rehabilitation intervention for cancer survivors. We selected cognitive rehabilitation techniques that addressed the most common complaints from survivors: memory and attention difficulties. These included memory techniques such as method of loci and attention techniques such as chunking and repetition. We hypothesized that treatment would result in improvements in quality of life related to cognition as well as objectively measured memory and attention performance.

* Corresponding author at: University of Washington, Box 358280 S-112 G.U., Seattle, WA 98195, USA.
E-mail address: cherrier@uw.edu (M.M. Cherrier).

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Materials and methods

Subjects

Participants were adult cancer survivors recruited from the area through referral from providers or via response to flyers. Inclusion criteria were: 1. Subjective concern about declines in cognitive functioning related to a diagnosis of cancer and/or cancer related treatment. This was obtained by asking participants the question "do you have concerns about your memory or other thinking abilities following cancer treatment?". Participants were required to answer yes to this question to meet these inclusion criteria. Additional details on the nature and severity of these difficulties were obtained using the FACT-cog to allow for quantification and comparison among participants. 2. Age greater than 18 years and less than 90 years. 3. Completion of active treatment for cancer (e.g., chemotherapy, radiation therapy and surgery) 6 months or more in the past. 4. Able to read English and participate in informed consent process. Exclusion criteria were: 1. Ongoing treatment for cancer (e.g., chemotherapy, radiation, surgery, etc.). 2. Unstable medical problems (such as unstable or untreated heart disease or hypertension, diabetes in poor control, respiratory disease complicated by hypoxia or hypercapnia, infectious illnesses, unstable thyroid dysfunction, and/or currently hospitalized). 3. History of, or current symptoms of, serious psychiatric disorder requiring antipsychotic medications or hospitalization. Mild symptoms of depression or stable anti-depressants, and anti-seizure medications were acceptable. Due to adverse effects of benzodiazepines on cognition, this class of anti-anxiety medication was not allowed (Ghoneim and Mewaldt, 1990). 4. Current substance abuse as defined by consuming 4 drinks or more per day or binge drinking (6 or more drinks in one night) within the past week. 5. History of or current neurological illness that significantly impacts cognition (e.g. stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, head injury, epilepsy). 6. History of a central nervous system tumor, due to known site specific cognitive deficits and variability of treatment modality effects that would require selection and study arm balance efforts beyond the scope of this preliminary study (Alomar, 2010; Gregor et al., 1996; Hahn et al., 2009; Harder et al., 2004; Salander et al., 1995) 7. A score of 25 or more on the Patient Health Questionnaire (PHQ-9) a measure of depression (Wittkampf et al., 2009). 8. A score of 26 or below on the Mini Mental Status Exam (MMSE) a screening measure of cognition (Folstein et al., 1975).

Study procedures

The study design was a randomized, controlled trial of a group based cognitive rehabilitation program. Participants underwent a phone screening followed by an in-person screening session (visit 1), including neurocognitive tests and symptom questionnaires, and a second baseline assessment (visit 2) of neurocognitive tests. The in-person screening visit (visit 1) began with the informed consent process and all participants signed a written consent form. All study procedures and materials were approved by the University of Washington/Fred Hutchinson Cancer Research Center Institutional Review Organization. Symptom questionnaires included those that assess the frequency and severity of cognitive, mood and physical symptoms.

Symptom measures included a quality of life scale related to cognition, the Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) (Jacobs et al., 2007). The FACT-Cog has three subscales: symptoms of perceived cognitive impairments with higher indicating fewer symptoms, perceived cognitive abilities in which a higher score indicates a rating of better cognitive abilities, and overall quality of life with a higher score indicating better quality of life as it relates to cognition. Additional measures include a depression symptom measure, the Patient Health Questionnaire (PHQ-9), for which a higher score indicates more symptoms of depression (Wittkampf et al., 2007), an anxiety symptom measure Beck Anxiety Inventory (BAI), in which a higher score indicates endorsement of more and/or more severe anxiety symptoms (Stanley et al., 1996), and a measure of fatigue symptoms, Functional Assessment of Chronic Illness Therapy — Fatigue (FACIT-Fatigue), with higher scores indicating a better quality of life and fewer fatigue symptoms (Cella, 1997).

The neurocognitive battery was comprised of standard objective measures of attention, memory, and executive functions using published versions along with modified, equivalent alternate versions to control for practice effects. Measures included Wechsler Adult Intelligence Scale—III (WAIS-III) subtests digit span and digit symbol (Wechsler, 1997). Digit span is a task of attention and working memory and involves hearing a series of digits and recalling them in the same order (forward) or in the reverse order (backward). A score is given for both forward and backward and a total score is generated with a higher score indicating better performance. Digit symbol is a task of psychomotor coordination, visual tracking, and working memory and involves rapid completion of a series of symbols according to a visible key, with higher scores indicating better performance. The Stroop test is considered a task of executive function and involves reading text, naming color blocks and the interference trial in which the pre-potent response of reading must be inhibited to name ink color. Time to complete is recorded so that a lower score is better performance (Delis et al., 2001). The Rey Auditory Verbal Learning test (RAVLT), is a task of verbal memory in which participants hear a word list and must recall it after several presentations and a short delay (Schmidt, 1996). Total recall across trials as well as the delay are recorded with a higher score indicating better verbal memory. Participants were also given a questionnaire (using a five point Likert scale) to assess their experience and satisfaction with the workshops.

The neurocognitive measures were administered twice prior to the start of the intervention or control periods to help reduce practice effects. Only the baseline (visit 2) was used for analysis.

After the screening visit, and determining eligibility, participants were randomized to active treatment (TX) or control (CL) (delayed treatment). However, participants were not informed of the randomization process and therefore they were blind to their treatment condition until completing the study. All participants were told that they would undergo treatment. Study personnel were aware of their assignment, however, study personnel who were involved in the assessment of cognition and administration of questionnaires were not involved in administering the treatment.

Treatment (TX) included seven consecutive workshop sessions lasting 1 h and delivered over seven consecutive weeks. Content of the workshops included memory aids (e.g. calendar, reminders, note-taking, study aids) as well as development of memory skills (e.g. habit formation, method of loci, chunking, learning names) and one session on mindfulness meditation. Group sessions typically involved a didactic portion in which new concepts were introduced, a practice portion in which participants could try out the new skills with other group members and a portion of time devoted to review of previous concepts. Participants were also given assignments to work on the outside of the group sessions (i.e. homework) that encouraged them to practice the skills learned in class. The control condition (CL) involved no intervention. Participants in the control condition were informed that a group was not readily available and that they would be assigned to a group at the next possible opening. All participants underwent a post-condition evaluation with neurocognitive measures and symptom questionnaires. For participants in the TX group, post-test was scheduled one to two weeks after completion of the group workshops and for the CL group this was scheduled 7–8 weeks after their baseline evaluation (visit 2).

Statistical analysis

Data was entered into SPSS statistical software and double checked for accuracy. Mixed model (group by time) repeated measure

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MANOVAs were used to measure change over time in the treatment group and interaction effects. To help control for family wise error rates, all cognitive tests were included in one MANOVA and all QOL and questionnaires were included in one. An intent to treat approach was not used, and therefore participants who dropped out were not included in the final analysis. All participants who completed two or more group sessions were included in the analysis. Additional descriptive statistics were computed (e.g. t-test, chi square) for describing the sample and measuring any differences between TX and CL groups after random assignment and between withdrawals and treatment completers and for assessing responses on the post-treatment questionnaire.

Results

Fifty three participants were screened by phone and of those 41 met the criteria for participating in the clinic based screening exam. Reasons for dropping from the study following the phone screening include not yet 6 months post-treatment, not interested in participating and difficulties with time constraints. Twenty-eight cancer survivors met criteria for inclusion in the study and completed all study procedures and four participants completed all study procedures but did not complete more than two group sessions. Reasons for not completing all study procedures at the time of this data analysis included: waiting to participate in a workshop that is compatible with personal schedule, cancer recurrence, other health factors, high PHQ-9 score, travel distance, decided not to participate, and time constraints. Reasons for not completing workshops included cancer progression, time conflicts, difficulty with travel distance, and moving residence.

Demographic, questionnaire and neurocognitive test results are indicated in Table 1. There were no significant differences between the treatment and control groups at baseline on any of the questionnaires, tests or demographic variables. Four participants who completed fewer than 2 sessions were not included in the analysis and did not differ from those who completed on any demographic variables (e.g. length from treatment, age, education, severity of cognitive impairment as measured by FACT-Cog). Participants on average completed 72% (five or more) of group workshop sessions with an average amount of 45 min of time spent on homework between workshop sessions.

Quality of life related to cognition

Only participants in the treatment group demonstrated a significant improvement over time on all subscales of the Fact-Cog $F(3,21)$ 5.66, $p < .01$, including the quality of life subscale of the FACT-Cog $F(1,23)$ 7.28, $p < .01$ and perceived cognitive ability $F(1,23)$ 7.17, $p < .01$. In addition, the treatment group demonstrated a decrease in perceived cognitive impairments $F(1,23)$ 18.33, $p < .01$, as well as an observed interaction effect for perceived cognitive impairments $F(1,23)$ 4.45, $p < .05$. The interaction effect is due to a sharper slope (increase) in the treatment group compared to the control group.

Satisfaction with treatment

Overall participants were very satisfied with the treatment they received. The responses on the post-workshop questionnaire indicated a significant rating ($p < .05$) (i.e. strongly agree) on the following items: 'a better understanding of how memory and attention work'; 'increased confidence about trying new solutions to address memory and attention difficulties'; 'learning new solutions for dealing with daily memory

Table 1
Demographics, questionnaires, and neurocognitive results: Means and standard errors.

Demographics	Treatment		Control		Total	Significance
N	12		16		28	–
Age	60.5 (2.3)		57.8 (3.8)		58.9 (2.4)	NS
Education	17.8 (0.5)		16.5 (0.5)		17.1 (0.4)	NS
MCQ	13.9 (SD = 12.6)		17.3 (SD = 11.4)		15.5 (SD = 12.0)	NS
Sex	F = 11; M = 1		F = 15; M = 1		F = 26; M = 2	NS
Years since treatment	5.04 (1.2)		4.64 (1.4)		4.84 (1.0)	NS
Treatment modalities						
Chemotherapy	12		13		25	NS
Radiation	5		8		13	NS
Surgery	8		14		22	NS
Measures	Pre	Post	Pre	Post		
Quality of life measures						
FACT-Cog cognitive quality of life	8.2 (1.4)	**9.9 (1.4)**	8.7 (1.1)	9.8 (1.2)	–	$p < 0.01$
FACT-Cog perceived cognitive abilities	15.8 (2.4)	**20.1 (2.3)**	16.2 (2.0)	17.1 (1.9)	–	$p < 0.01$
FACT-Cog perceived cognitive impairment	35.7 (6.3)	**51.0 (5.7)**	37.7 (5.1)	42.9 (4.7)	–	$p < 0.01$
Mood and symptom measures						
FACIT-Fatigue	17.4 (2.7)	13.5 (1.9)	20.9 (2.8)	17.2 (2.0)	–	NS
PHQ9	5.7 (1.6)	4.5 (1.2)	7.2 (1.7)	6.6 (1.3)	–	NS
BAI	6.2 (1.9)	4.3 (1.4)	8.6 (2.0)	7.9 (1.5)	–	NS
Neurocognitive tests						
RAVLT-total trials 1–5	29.8 (1.7)	29.4 (1.4)	27.4 (1.5)	27.9 (1.2)	–	NS
RAVLT delay	10.4 (0.7)	10.7 (0.7)	9.6 (0.6)	9.3 (0.6)	–	NS
Stroop interference trial	61.1 (4.3)	54.0 (4.8)	57.8 (3.7)	55.9 (4.3)	–	NS
Digit symbol	69.1 (4.3)	72.0 (3.9)	70.9 (3.7)	70.9 (3.4)	–	NS
Digit span forward	10.6 (0.5)	11.4 (0.6)	9.4 (0.5)	9.6 (0.5)	–	NS
Digit span backward	7.5 (0.5)	**9.8 (0.6)**	6.7 (0.5)	7.4 (0.5)	–	$p < 0.01$
Digit span total	18.1 (0.9)	**21.3 (1.1)**	16.1 (0.5)	17.0 (1.0)	–	$p < 0.01$

Significant results are indicated in bold and occurred only in the treatment group.
Medical Comorbidities Questionnaire (MCQ) — Total score, higher score indicates more medical co-morbidities; Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) — Total score, higher score equals better QOL; Patient Health Questionnaire-9 (PHQ9) total score, higher score indicates more severe depression symptoms; Beck Anxiety Inventory (BAI) — total score, higher score indicates more severe anxiety symptoms; Rey Auditory Verbal Learning Test (RAVLT) raw scores, higher score indicates better verbal memory; Stroop raw score (Seconds to completion) higher is worse performance; digit symbol raw score — higher score is better performance; digit span raw score-higher score is better performance; FACT — Functional Assessment of Cancer Therapy-cognition (FACT-Cog) — cognitive subscale scores, QOL — higher score equals higher quality of life, perceived cognitive abilities — higher score indicates a higher perception of abilities, perceived cognitive symptoms — higher score indicates fewer adverse symptoms.

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failures'; and a (agree) rating ($p < .05$) for 'overall I am better able to cope with cognitive difficulties'.

Mood, anxiety and symptom measures

As anticipated, we did not observe a significant change in measures of fatigue (FACIT) or depression (PHQ-9) or anxiety (BAI). We did not expect that these would change as a result of our intervention targeted at cognitive functioning.

Neurocognitive tests

Participants in the treatment group demonstrated a significant improvement from their baseline in attention as measured by digit span backward and the digit span total score $F(7,20)$ 4.197, $p < .01$. Improvements in the treatment group were also noted on digit span forward, RAVLT total recall over three trials, RAVLT delayed recall, Stroop test (interference trial) and digit symbol. However, these changes were not significantly different from baseline, although delayed recall on RAVLT was a trend finding ($p < .10$).

Discussion

This study was a preliminary examination of the efficacy of cognitive rehabilitation workshops on cognitive function in cancer survivors with subjective report of cognitive dysfunction. We developed a group based cognitive rehabilitation program, designed for cancer survivors, based on successful components of previous cognitive rehabilitation studies that included new restorative cognitive strategies as well as compensatory aids. Our findings indicate that participants in the treatment group evidenced improvements in objective measures of neurocognitive functioning with a significant change compared to baseline for a measure of attention (digit span). Significant improvement was not observed on all measures.

Participants demonstrated improvement in both the digit span total score and digit span backward. Backward digit span is often considered a working memory task as well as a task of attention (Elliott et al., 2011). Working memory can be described as our mental scratchpad. It allows us to hold information in temporary space and also allows the cognitive manipulation or calculation with the information (Osaka et al., 2007). Studies have shown that working memory may in fact be smaller than the originally hypothesized seven plus or minus two, and may in fact be four plus or minus one (Cowan, 2001). Although working memory is generally thought to be limited in capacity, according to a model proposed by Cowan, it can be considered part of a larger memory system and therefore expanded through the use of additional strategies such as chunking (Fendrich and Arengo, 2004; Huntley et al., 2011). Chunking of information is one of the skills taught in the cognitive rehabilitation workshops, so it is not surprising that this skill improved. If working memory can be considered as one aspect of an overall memory system, then participants are likely to demonstrate other areas of memory improvement. An improvement on recall for a verbal list learning task was also observed. Although this change was at trend level and therefore did not achieve significance, it demonstrates that improvements were consistent in the domains of memory and attention across several tests.

In addition, we hypothesized that treatment would result in perceived improvements in quality of life related to cognition. Participants demonstrated a significant improvement in their self-ratings on the FACT-Cog subscales. The FACT-Cog was developed to assess cognitive complaints in cancer patients with a similar scoring system as the functional assessment of cancer therapy scoring system. The FACT-Cog includes items such as "I have had trouble concentrating" and "My mind is as sharp as it has always been" which are rated on a seven point Likert scale according to how accurate the statement has been over the past week. There are three subscales to the FACT-Cog, one that relates to cognitive abilities, one that relates to cognitive impairments and one that relates to overall quality of life in regard to cognitive functioning. Participants in the treatment group demonstrated an improvement on the perceived cognitive impairments subscale indicating a decrease in their cognitive impairments. They also demonstrated an improvement in their cognitive abilities as measured by the perceived cognitive ability subscale, and an improvement on the impact of perceived cognitive impairments on quality of life. These changes in the quality of life related to cognitive difficulties are important and provide a measure of the global impact of our intervention on the overall quality of life and with regard to common daily cognitive activities. The FACT-Cog findings are consistent with our post-treatment questionnaire, in which participants were asked to rate changes in cognition and their satisfaction with the intervention. Participants in the treatment group indicated strong agreement with having a better understanding of how memory and attention work, and having learned new solutions for dealing with daily memory failures as well as feeling more confident about trying new solutions to address cognitive difficulties.

It has been suggested that cognitive impairments may be impacted by mood and emotional factors. Clinically significant elevations in depression and anxiety measures prior to, during and following treatment are not unusual (Alcalar et al., 2012; Iconomou et al., 2004), and several studies have supported a relationship between mood and anxiety and cognition independent of cancer (Lee et al., 2012; Vasudev et al., 2012). Mood and anxiety symptom measures taken at baseline prior to treatment were in the mild range at the start of treatment and did not change as a result of the intervention. Thus, our findings do not indicate an influence of cognitive rehabilitation on symptoms of depression and anxiety as measured by traditional mood measures. However, it has been shown that other cognitive behavioral interventions may have a beneficial effect on cognition in cancer survivors (Ferguson et al., 2007, 2012). Thus, additional work with regard to the relationship between mood mediators and cognition is needed.

The present study design had several strengths including two testing sessions prior to the start of treatment as well as randomization to the treatment and control conditions. Given the evidence of practice effects over a short duration, efforts to control these effects are important in studies that objectively measure cognition (Lezak, 1995).

Despite the strengths in our study design, our results are limited by a relatively small sample size, and should be replicated with a larger sample size and an active control if possible. We did not observe significant changes in all of our measures for the treatment group and one of the FACT-Cog subscales (FACT-Cog QOL) despite improvement was comparable between the treatment and control at the post-timepoint. Our control condition was a wait-list condition, in which participants were told that they would be included in treatment once it was available. It is possible that post-treatment differences of self-reported symptoms on the FACT-cog may reflect treatment expectancies mixed in with treatment effects as the control group was aware that they did not receive treatment. An active control would have been a stronger study design. An active control would deliver a treatment that satisfies the expectation of treatment without the specifics of the treatment under evaluation. A future study will need to incorporate an active control condition in which participants anticipate and participate in some form of treatment. Our findings of improvement on an objective measure of cognitive function lend some confidence to our results in light of this design weakness.

Participants in this study were enrolled based on self endorsement of cognitive dysfunction. An examination of baseline cognitive scores reveals performance ranging from mild weakness to normal and above average performance. It is possible that improvement in the treatment group might have been more robust by selecting participants for impairment at baseline. However, this selection approach was not utilized in this sample of cancer survivors for several reasons including: 1) It was anticipated that participants would not perform perfectly or well above average on *all* objective measures, and therefore there would be room

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for measureable improvement. 2) Given that many cancer survivors are older it was anticipated that the average age of our sample would also be older. The modal age of our sample was age 68. As the onset of dementia sharply increases after age 65, selecting a sample of adults with cognitive impairments in that age range increases the risk of selecting for dementia. Thus the decision was made to recruit participants based on their subjective endorsement of cognitive difficulties rather than objective evidence of impairment.

This study did not include a formal analysis with regard to missing data biases (Jo, 2007; Little et al., 2012). Certainly the issue of missing data and adherence to treatment is important in clinical treatment studies and behavioral treatments. Participants on average completed 72% or more of the workshop sessions. In addition, four participants completed two or fewer workshop sessions. Thus, adherence to treatment may be challenging for patients. Participants who dropped from the study cited issues of scheduling (e.g. schedule changed and unable to attend groups or difficulties with work/social role demands that compromised attendance) or transportation (e.g. found that traffic was impeding ability to attend after work). Consideration for additional ways to make participation more attractive or convenient should be considered for future studies. Although we utilized a measure of time spent on homework as a measure of adherence, additional self-rating measures may be beneficial. A larger study with an active control will allow a more sophisticated analysis of missing data bias. Our analysis did not include study drop outs and therefore may slightly overestimate treatment effects, although this was not directly modeled.

Conclusion

These results suggest that cognitive rehabilitation may be an effective treatment for cancer survivors who are struggling with symptoms of cognitive dysfunction. Our results are consistent with the previous findings of improved cognition from a cognitive-behavioral study in cancer survivors (Ferguson et al., 2007, 2012). Additional research in this important area needs to be conducted to determine the optimal type of treatment that is effective for cancer survivors.

Conflict of interest statement

Q6 Authors report no conflicts of interest for this project or manuscript.

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C. Higano, H. Gray, S. Willis and D. David participated in the manuscript preparation and data analysis, and A. Church and K. Anderson participated in the aforementioned plus protocol implementation and data collection and M. Cherrier participated in all of the aforementioned plus study design.

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The project described in this manuscript was conducted within the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans http://www.wma.net/en/30publications/10policies/b3/index.html.

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