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Association of Fatigue Intensification with Cognitive Impairment during Radiation Therapy for Prostate Cancer

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Abstract

Purpose

Cancer-related fatigue is a common complaint during cancer treatment and is often associated with cognitive impairment. This study examined cognitive deficits that were associated with fatigue symptoms during external-beam radiation therapy (EBRT) in men with localized prostate cancer.

Methods

A total of 36 participants were enrolled and followed up at baseline, 24 h, 7 days, 14 days after EBRT initiation, at midpoint, and at completion of EBRT. Fatigue was measured by self-report using the Functional Assessment of Cancer Therapy – Fatigue (FACT-F), and cognitive impairment by the Computer Assessment of Mild Cognitive Impairment (CAMCI®).

Results

Subjects with increased fatigue during EBRT reported a significant decline in cognitive function and had difficulties with CAMCI®'s route finding and item recall tasks during EBRT. Increased fatigue during EBRT was associated with perceived cognitive difficulties in executive function and recognition memory, but not with attention or verbal memory.

Conclusions

Our results suggest that there might be specific cognitive domains that are associated with increased fatigue during EBRT. These findings will provide important information for targeting specific cognitive domains using pharmacotherapy or behavioral interventions. CAMCI® is a valuable tool for psycho social providers to detect subtle cognitive impairment in fatigued cancer patients in a clinical setting.

Keywords: Cancer-related fatigue, Radiation therapy, Prostate cancer, Cognitive impairment

Introduction

Cancer-related fatigue, a "distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [1], is among the most troublesome and frequently reported side effects of cancer and cancer treatment [1, 2, 3, 4]. Cancer-related fatigue has been shown to worsen progressively during cancer therapy, including radiation therapy, and may last up to years after treatment completion [5, 6]. Despite its prevalence and negative impact on patients' health-related quality of life, fatigue is a symptom often underdiagnosed and poorly managed [4, 7].

Among the major complaints of fatigued cancer patients is cognitive impairment, which often develops during or after cancer treatment [8, 9, 10]. The previous lit erature has mostly focused on cognitive impairment in fatigued cancer patients after receiving chemotherapy or adjuvant therapy [9, 11, 12]. For example, cancer survivors often report posttreatment cognitive difficulties which tend to be diffuse in the domains of attention, concentration, verbal and visual memories, as well as processing speed, and working memory [8, 11, 13]. In addition, fatigue, cognitive impairment, and depression often co-occur in cancer patients after receiving chemotherapy, possibly due to chemotherapeutic agent-related systemic toxicity as well as direct neurotoxicity [13, 14, 15]. However, cognitive impairment in patients treated with localized, noncranial radiation therapy without any chemotherapy is relatively less explored [16, 17, 18]. In addition, cognitive deficits in cancer patients are typically assessed using the standard paper-and-pencil tests or in-person interviews, which are time-consuming and labor intensive for patients who are already fatigued [19, 20]. Further, self- reported (or perceived) cognitive deficits do not always reflect a subject's performance on neuropsychological (or objective) tasks [21, 22, 23]. Therefore, there is a need to develop objective cognitive tests that correspond to subjective cognitive impairments that can be useful for cancer patients.

Our goal in this study was to assess cognitive deficits associated with worsening of fatigue symptoms during external-beam radiation therapy (EBRT) in men with localized prostate cancer. Previous studies reported deficits in processing speed and attention associated with fatigue in patients with disorders including chronic fatigue syndrome and multiple sclerosis [24, 25]. Therefore, we hypothesized that changes in fatigue symptoms during EBRT would be related to changes in cognitive function as demonstrated by altered task performance reaction time and attention issues using the Computer Assessment of Mild Cognitive Impairment (CAMCI®) (Psychology Software Tools, Inc., Sharpsburg, PA, USA), which is a self-administered computer-based tool developed to measure cognitive function [26]. We also aimed to test the feasibility of using CAMCI® in a clinical setting to determine specific cognitive domains that are associated with changes in fatigue symptoms during EBRT.

Methods

Participants

The current study (NCT00852111) was approved by the Institutional Review Board (IRB) of the National Institutes of Health (NIH), Bethesda, MD, USA. All participants enrolled in this study were men, 18 years of age or older, diagnosed with nonmetastatic prostate cancer with or without prior prostatectomy, and scheduled to receive EBRT. The entire EBRT treatment lasted 38–44 days, depending on the clinical stage of the prostate disease.

Patients with chronic inflammatory disease, an unstable or end-stage disease of any body system, a major psychiatric disorder within the past 5 years, an infectious disease such as HIV and hepatitis, or a second malignancy were excluded from the study. Those receiving chemotherapy or taking medications known to affect cytokine production, such as tranquilizers, steroids, and nonsteroidal anti-inflammatory agents, were also excluded from this study in order to avoid confounding contributions of these factors to cognitive performance [27, 28].

Subjects were recruited from September 2009 to November 2014 at the Magnuson Clinical Research Center at the NIH. Signed written informed consent was obtained prior to study participation.

Instruments

Clinical and demographic data (e.g., age, race, stage of prostate cancer, EBRT dose, EBRT technique used, and laboratory tests) were obtained by chart review at baseline (prior to EBRT initiation) and at days 19–22 or at midpoint of EBRT. Fatigue was assessed at baseline, 24 h (1 day), 7 days (1 week), and 14 days (2 weeks) after EBRT initiation, at midpoint, and at completion of EBRT, using the frequently administered 13-item Functional Assessment of Cancer Therapy – Fatigue (FACT-F), a validated, reliable, stand-alone measure of fatigue in cancer therapy (the questionnaire items and scoring method can be found at www.facit.org) [29]. FACT-F has good internal consistency reliability with Cronbach's $\alpha = 0.81$ when tested in our study participants. The FACT-F questionnaires were administered by investigators experienced with FACT-F administration in an outpatient setting before the clinical procedures began in order to avoid extraneous influences on the responses. Each item response is rated on a 0–4 scale, where a 0 represents “not at all” and a 4 indicates that the respondent relates to the corresponding statement “very much.” Total FACT-F scores can range from 16 to 53, with lower scores reflecting higher fatigue intensity. Subjects were considered to have significantly increased fatigue when there was a decrease in FACT-F score of ≥3 points from baseline to midpoint of EBRT (increased fatigue [IF]: $\text{FACT-F}_{\text{midpoint}} - \text{FACT-F}_{\text{baseline}} \geq 3$; stable fatigue [SF]: $\text{FACT-F}_{\text{midpoint}} - \text{FACT-F}_{\text{baseline}} < 3$). The 3-point change in FACT-F score satisfies the minimally important difference threshold which has been shown to be clinically meaningful (defined by Cohen's 0.2- to 0.5-SD effect sizes) [30, 31, 32].

The Revised Piper Fatigue Scale (rPFS) is a 22-item multidimensional questionnaire that measures four domains of fatigue: (1) behavioral (6 items related to the severity, distress, and degree of disruption in activities of daily living); (2) affective (5 items related to the emotional meaning attributed to fatigue); (3) sensory (5 items related to the physical symptoms of fa-

tigue); and (4) cognitive/mood (6 items related to mental and mood states) [33, 34]. When tested in our patient population, rPFS has excellent internal consistency reliability with Cronbach's α = 0.97; each item is coded on a 0–10 numeric scale and each subscale is scored individually [35, 36]. In particular, the rPFS cognitive/mood subscale has been used in studies to quantify perceived cognitive impairment/mood change in various patient populations [34, 37, 38]. To determine subjective cognitive difficulties, this study used the rPFS cognitive/mood subscale score, which is calculated as the average of the responses from items that asked participants to what degree they are now feeling related to being (1) patient or impatient, (2) relaxed or tense, (3) exhilarated or depressed, (4) able to concentrate or unable to concentrate, (5) able to remember or unable to remember, and (6) able to think clearly or unable to think clearly.

To control for potential confounders that may affect cognitive performance, sleep disturbance and depressive symptoms were measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance (PROMIS-SD) short form, and the Hamilton Depression Rating Scale (HAM-D) [39], respectively. PROMIS-SD was developed as part of the NIH Roadmap Initiative from more than 1,000 data sets from multiple disease populations (www.nihpromis.org). The PROMIS-SD short form consists of 8 items and has demonstrated good validity (0.83) and internal consistency (Cronbach's α > 0.90) [40, 41]. The PROMIS measures are reported on a T-score metric that is anchored to the mean score of a healthy American general population [42]. HAM-D is a validated, 24-item questionnaire commonly used to assess depressive symptoms with scores ranging from 0 to 54, with high scores reflecting severe depression; a score of 0–7 indicates no depression, a score of 8–16 indicates mild depression, and a score of ≥17 indicates moderate-to-severe depression [43]. HAM-D has good internal consistency (standardized Cronbach's α = 0.67–0.80) and test-retest reliability (Pearson correlation coefficient = 0.88, $p < 0.001$) [44].

The Stroop Color-Word Interference test was administered on a PC laptop with four color-coded keys (Left Response – red and green; Right Response – blue and yellow) to measure change in attention and processing speed from baseline to the midpoint of EBRT. The Stroop test is a widely used tool in medical research and has shown good reliability and validity (with a test-retest correlation of 0.83–0.91); it has been used in previous studies to test cognitive deficits in cancer patients [45, 46, 47]. There were a total of 7 blocks with breaks in between, and the entire task took 15–20 min for the subjects to complete. A block consisted of a continuous series of color word or control prompts. Each prompt was displayed in red, green, blue, or yellow font color against a black background for a maximum of 1,500 ms. The next prompt was displayed as soon as the subject made a selection or if the subject did not respond within 1,500 ms. For each block, the subject was instructed to quickly press the color-coded key that corresponded with the font or ink color displayed on the screen. There were three types of testing blocks: congruent, incongruent, and control. In a congruent block, the font color and word prompt matched. In an incongruent block, the font color and word prompt did not match. In a control block, a non-color word prompt would appear in one of the four possible font colors.

CAMCI® Administration

CAMCI® (Psychology Software Tools, Inc., Sharpsburg, PA, USA) is a self-administered, tablet computer-based tool that can be completed in 20 min [26]. CAMCI® has good test-retest reliability and has demonstrated good sensitivity (86%) as well as specificity (94%) for the identification of mild forms of cognitive impairment [26, 48]. The sensitivity of CAMCI® was 0.72 relative to the Global Impairment Rating, with good positive and negative predictive values of 0.93 and 0.89, respectively [49]. CAMCI® was administered in English on a touch screen tablet PC at baseline, at midpoint, and at completion of EBRT. The CAMCI® tablet utilizes a virtual reality environment (see Fig. 3a) to test a subject's cognitive ability in multiple domains including reaction time, memory accuracy, implicit memory, and declarative memory.

Subjects not proficient in English, as determined by an IRB-approved English Proficiency Assessment, were excluded from taking the CAMCI®. Once the administrator entered and verified the subjects' information (research ID, gender, and educational level), each subject was asked to follow the written (in large fonts) and verbal prompts from the tablet using a stylus pen. At the start of CAMCI®, the subjects were prompted to select “yes” or “no” on the following self-report questions: whether they (1) experienced memory loss, (2) were currently using alcohol, experienced (3) depression and (4) anxiety, (5) were driving or (6) had ever driven, (7) had ever used a computer, or (8) had ever used an automated teller machine (ATM). The subjects were informed that the assessment must be completed in one continuous, uninterrupted session. Additional assistance was only given by the administrator if a participant needed logistical assistance (e.g., using the stylus and repositioning the tablet). The CAMCI® scores for each task are presented in percentile format [26, 50]. The following tasks are included in CAMCI® [49].

Star Task. The subjects were shown a variety of shapes and were instructed to respond by tapping the screen as soon as they saw the star shape.

Digit Span Forward. A series of 3–6 digits were presented 1 digit per second. The subjects were then instructed to recall the digits in the correct order.

Digit Span Reverse. A series of 3–6 digits were presented 1 digit per second. The subjects were then instructed to recall the digits in the reverse order.

Word Recall. The subjects were shown a list of five 3-letter words on the computer to remember. These 5 words were shown 3 times, one at a time. About 10 min after the learning phase, the subjects were instructed to recall those 5 words and type them on the computer.

Word Recognition. The subjects were instructed to remember a list of 6 multisyllabic words which were shown on the computer one at a time. After about 10 min, the subjects were instructed to select the word that was previously shown from a set of 6 phonemically related words. There were a total of 6 sets of words with 6 words per set. The number of correct answers, as well as the amount of time it took for the subject to recognize the words, was recorded.

Visual Memory. The subjects were shown a series of images in a fixed order. Then they were shown a new series of images and were then instructed to select “yes” or “no” depending on whether they had previously seen the image.

Go/No-Go Test. In the first task, the subjects were instructed to tap the screen twice when they heard 1 beep and tap the screen once when they heard 2 beeps. In the second task, the subjects were instructed to tap the screen twice when they heard 1 beep but do nothing when they heard 2 beeps.

Virtual Reality Shopping Trip. (1) The subjects were provided with directions to the grocery store and were asked to decide which direction to go at each intersection. (2) While driving to the grocery store, the subjects passed several objects (a car, a bus, or a boy on a bicycle) without being instructed to remember them. After the trip, the subjects were shown a series of images and were instructed to select the ones they had previously seen. (3) The subjects were told at the beginning of the trip that they would stop at the bank to transfer money and stop by the post office to mail a letter on the way to the grocery store. While driving in the virtual reality environment, the subjects were supposed to tap on the bank and post office as they appeared on the screen. At the bank, the subjects were shown an ATM machine and were instructed to transfer USD 250 from the savings account to the checking account. After tapping on the post office sign, the car drove by the mailbox and the letter was sent automatically. (4) The subjects were instructed to purchase a list of grocery items (i.e., bread, bananas, donuts, and shampoo) in the beginning. When the subjects arrived at the grocery store at the end of the virtual reality shopping trip, they were shown various images of grocery items and were instructed to select the correct ones to purchase.

Statistical Analysis

Descriptive analyses were used to describe the demographic characteristics of the sample. Categorical variables such as education, ethnicity, T stage, Gleason score, and androgen deprivation therapy (ADT) usage were analyzed using the χ^2 test for association, whereas variables such as age, BMI, and PSA level were compared using the two-tailed *t* test. All data are expressed as the mean ± standard error of the mean (SEM).

Post hoc power analysis of the primary outcome of the study, with power set at 0.80 and α set at 0.05 (two-tailed), showed that a sample of 32 subjects would be required to reach a statistical significance at 0.05. With the actual sample size of the study ($n_{\text{increased fatigue}} = 20$, $n_{\text{stable fatigue}} = 16$) included in the post hoc power analysis, the observed power ($\alpha = 0.05$) was 84.7%, indicating that the sample size used in the study was sufficient.

Repeated-measures analysis of variance (ANOVA) was employed to assess the effects of time on fatigue levels and cognitive tasks. The sphericity assumption was first checked using Mauchly's test of sphericity prior to conducting repeated-measures ANOVA. For analyses of cognitive task performance between groups, Levene's test of homogeneity of variance was first performed, and when Levene's test of homogeneity of variance was violated (significance < 0.05), the data were analyzed using nonparametric tests of significance. Analysis of covariance (ANCOVA) with age, education, BMI, race/ethnicity, cancer T stage, HAM-D score, and PROMIS-SD score as covariates was performed to compare scores of specific items in CAMCI®. Post hoc between-group comparisons were performed using Mann-Whitney U tests with false discovery rate correction for multiple comparisons. Statistical analyses regarding fatigue symptoms were conducted with SPSS statistics software version 20 (IBM SPSS, Purchase, NY, USA).

Results

Subject Demographics

A total of 36 subjects with localized prostate cancer (T stages 1–3) who completed all study procedures from baseline (before EBRT) to EBRT completion (Table 1) were included in the analyses. The final participant cohort was predominantly Caucasian (63.89%) with an average age of 66.50 ± 1.17 years and a BMI of 30.07 ± 0.73 (Table 1). Most of the subjects had either bachelor's degrees (36.11%) or advanced degrees (25%).

The majority of the subjects (94%) had experience using a computer, driving (100%), and using an ATM (79%) (Table 2). Mild anxiety was found in 18% of the participants before EBRT and in 13% during treatment. Mild depressive symptoms were found in 9% of the participants prior to EBRT and in 3% during EBRT. Alcohol use (participants answered either “yes” or “no”) was reported by 3% of the subjects at baseline and by 0% during EBRT.

Trajectory of Fatigue

Overall, the subjects did not experience fatigue at baseline (FACT-F score = 45.53 ± 1.21), using a cutoff FACT-F score of < 43. A FACT-F score of 43 was previously reported as the average score of the general US population [6, 30]. Fatigue increased significantly 2 weeks after EBRT initiation and over time ($F(5, 294) = 3.69$, $p = 0.03$), reaching a peak at the midpoint of EBRT (Fig. 1a). Using the definition of increased fatigue described in the Methods section [31], 55.5% ($n = 20/36$) of the entire sample experienced a clinically relevant increase in fatigue symptoms during EBRT. The fatigue scores of these IF subjects significantly worsened (IF: $\text{FACT-F}_{\text{midpoint}} - \text{FACT-F}_{\text{baseline}} \geq 3$, $n = 20$, $p = 6.08 \times 10^{-7}$) compared to the SF subjects (SF: $\text{FACT-F}_{\text{midpoint}} - \text{FACT-F}_{\text{baseline}} < 3$, $n = 16$, $p = 0.69$) from baseline to the midpoint of EBRT. Even though the baseline FACT-F scores of the two groups were similar and did not meet the cutoff threshold for fatigue [30] ($\text{FACT-F}_{\text{IF}}$ score = 45.35 ± 1.39, $\text{FACT-F}_{\text{SF}}$ score = 45.75 ± 2.14, $p = 0.87$), the midpoint FACT-F scores of the IF group were significantly lower compared to those of the SF group ($\text{FACT-F}_{\text{IF}}$ score = 34.85 ± 1.85, $\text{FACT-F}_{\text{SF}}$ score = 46.94 ± 1.87, $d = 1.65$, $p = 6.08 \times 10^{-7}$) (Fig. 1b). The IF and SF subjects did not differ significantly ($p > 0.5$) in their demographic or clinical characteristics, such as age, BMI, and PSA levels (Table 1). ADT was used by 85% of the IF subjects and 62.5% of the SF subjects.

Trajectory of Cognitive Function and Correlation with Fatigue

Of all study measures, only subjective cognitive function and mood alterations, as measured by the rPFS cognitive/mood subscale, correlated with FACT-F scores at baseline ($r = -0.602$, $p = 0.000006$). In addition, subjective cognitive decline as well as alterations in mood associated with fatigue significantly increased over time during EBRT in the entire sample ($F(4, 186) = 5.92$, $p = 0.0001$). No significant change in reaction time between the study time points was observed using the Stroop test.

Compared to the SF subjects, the IF subjects reported significantly worsened cognitive difficulties ($d = 1.28$, $p = 6.71 \times 10^{-6}$) using the self-reported rPFS – cognitive subscale (Fig. 2a). No difference in reaction time between the IF and SF participants was observed on the Stroop test

in either the congruent or the incongruent condition ($p > 0.05$) (Fig. 2b). At the midpoint of EBRT, by which time fatigue had significantly increased, the IF subjects had more trouble with spatial memory in the route finding task ($d = 0.86$, $p = 0.04$) (Fig. 3b) and with memory accuracy in the item recall task than the SF subjects ($d = 1.07$, $p = 0.02$) (Fig. 3c). Interestingly, during the peak of fatigue (midpoint of EBRT), fatigue scores correlated with speed ($r = 0.46$, $p = 0.009$) but not with accuracy in the word recognition task (Fig. 3d). We also assessed the overall performance of all subjects in each CAMCI® task over time and found a significant learning effect ($F(2, 22) = 8.13$, $p = 0.002$) (Fig. 4).

Discussion

The major finding in this prospective study of fatigue in subjects treated with EBRT for prostate cancer was that 55.5% of the entire sample experienced increasing fatigue during EBRT. Subjects with increased fatigue reported worse cognitive deficits and significantly more difficulties performing the cognitive tasks of route finding and itemized recall compared to subjects with stable fatigue. These findings not only provide empirical support that fatigue is associated with deficits in cognitive functioning, but also suggest that fatigue negatively impacts executive function, explicit memory, and word recognition processing speed.

CAMCI® was well tolerated by all subjects in the study. Although CAMCI® is not a comprehensive cognitive test, it provides an easy-to-use and sensitive tool for assessing cognitive difficulties in cancer patients in a clinical setting. Compared to the traditional paper-and-pencil tests, CAMCI® does not require a clinician to administer and score the test, and thus is easily adaptable to a clinical setting. It is also well tolerated by elderly patients with limited computer knowledge and can be completed in 20 min [26]. Furthermore, CAMCI® is a sensitive tool for detecting mild cognitive problems in nondemented patients [26, 49]. To demonstrate the sensitivity of CAMCI® in discerning cognitive difficulties in the cancer population, we incorporated the Stroop test in our study, as it is a widely used test across multiple disciplines including cancer-related fatigue [51]. Although no difference between IF and SF subjects in the Stroop test was detected, performance in specific CAMCI® tasks was significantly compromised in the IF subjects compared to the SF controls, which is consistent with the self-reported subjective cognitive impairment related to fatigue.

Despite its sensitivity, because CAMCI® is designed to be tolerated by older adults and the tasks are relatively simple, there is a significant learning effect over time (Fig. 4). Therefore, studies involving short intervals of CAMCI® tests need to employ further statistical adjustments, including a reliable change index, to counteract practice effects. As a relatively new tool compared to other commonly administered psychometric screening tools such as the Mini-Mental State Examination (MMSE), CAMCI® still needs to be validated longitudinally in larger samples in future studies. Further, future studies involving comprehensive comparisons of CAMCI® with other cognitive impairment tools will allow researchers to better evaluate the validity of using CAMCI® as a routine measure of cognitive functions in a clinical setting.

We evaluated the clinical feasibility of using CAMCI®. Contrary to findings from previous fatigue studies in other disease conditions including chronic fatigue syndrome and multiple sclerosis [24, 25], perceived cognitive impairment in the participants with prostate cancer during radiation therapy in this study was not associated with reaction time or attention using the Stroop test, nor was it related to issues with verbal memory and working memory as mea-

sured by CAMCI®. This may be related to differences in severity or chronicity of the fatigue condition experienced by these clinical populations and the use of different instruments to measure cognitive function. However, it is noteworthy that subjects with increased fatigue did not perform worse than subjects with stable fatigue on memory tasks, suggesting that fatigue may be dissociable from memory impairment.

As a group, the subjects did not exhibit an advantage on verbal recognition over verbal recall (Fig. 4), possibly due to the different difficulty levels of the tests in CAMCI®. The word recall test includes a set of five 3-letter, single-syllabic words, while the word recognition test includes a set of 6 multisyllabic words which were presented during the learning phase, and all subjects were later instructed to select the correct words among other phonemically related words. In addition, the word recall test was administered early in the series of tests, whereas the word recognition test was administered several tests after the word recall test, possibly imposing a heightened level of difficulty in the word recognition test related to possible memory interference. Future studies will need to select an instrument that will have comparable difficulty levels in the verbal recall and verbal recognition tests. One caveat of the study is that a higher percentage of fatigued subjects received concomitant ADT (85%) compared to SF subjects (62.5%). Concomitant ADT use has been linked to impaired cognitive performance in prostate cancer patients [52, 53]. In addition, we have shown previously that ADT was a reliable clinical predictor of fatigue during radiation therapy for prostate cancer [5]. Future research using large samples should investigate the influence of ADT use on the relationship of cognitive decline and fatigue during radiation therapy. Because factors such as anxiety or depressive symptoms may also influence cognition, we excluded clinically depressed individuals (HAM-D score ≥8) from the study to avoid confounding [43]. Another caveat is that the rPFS cognitive/mood subscale used in this study does not differentiate between cognitive impairment and mood disorder. However, rPFS is a widely used, multidimensional tool that measures different domains of cancer-related fatigue, including its cognitive domain [36, 54]. With the small window of time allowed to assess the study participants, it was not possible to use a more comprehensive and traditional measure of cognitive function. Because of the observed difference in rPFS cognitive/mood subscale scores between IF and SF subjects and the time constraint associated with study outcome administration, we incorporated CAMCI® as a study measure to further assess cognitive impairment associated with fatigue.

Many studies including the current study have demonstrated associations between fatigue and cognitive alterations, but the majority of these studies are cross-sectional. It is not clear whether cognitive deficits precede fatigue, or act as a causal factor. The purpose of this study was not to use CAMCI® to assess temporal changes in cognitive performance and fatigue. Future research using temporally stable cognitive assessments is needed to understand the temporal order of fatigue and changes in the brain. In addition, future research using both behavioral tests and functional imaging is needed to unravel how EBRT is related to fatigue, cognitive changes, and structural and functional changes in the brain.

Perceived cognitive difficulties are common in patients who experience fatigue during cancer treatment. Because perceived cognitive impairment does not always reflect objective cognitive performance [21, 22], it is imperative to supplement cognitive function assessments that rely on self-report with more objective tests. While CAMCI® is a relatively new tool, it allows clinicians to quickly assess specific domains of cognition that patients have trouble with. Although

CAMCI® may not be used as a stand-alone diagnostic tool for cognitive impairment, the information obtained from CAMCI® tests would provide important information for further follow-up in a more targeted fashion.

In conclusion, increasing fatigue in prostate cancer subjects during EBRT is associated with perceived cognitive difficulties. Specifically, increased fatigue in these subjects was associated with impairment in executive function and recognition memory, but not with attention, reaction time, or verbal memory. These findings will provide important information for targeting specific cognitive domains using pharmacotherapy or behavioral interventions. CAMCI® is a valuable tool for detecting subtle cognitive impairment in fatigued cancer patients in a clinical setting, though further validation of its clinical utility in longitudinal assessments is needed.

Disclosure Statement

The authors declare no conflict of interest.

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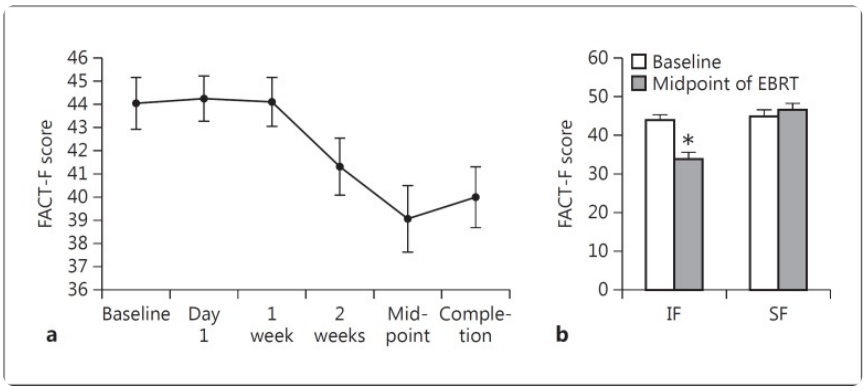
Figures and Tables

Fig. 1



Fatigue increased with external-beam radiation therapy (EBRT). **a** The FACT-F (Functional Assessment of Cancer Therapy – Fatigue) scores of the cohort (n = 36) decreased over time (baseline or prior to EBRT initiation, 1 day after EBRT, 1 week after EBRT, 2 weeks after EBRT, midpoint of EBRT, and com pletion of EBRT), reaching the lowest point at midpoint of EBRT. $F(5, 294) = 3.69$, $p = 0.03$. **b** Subjects were considered to have significantly increased fatigue (IF) when there was a decrease in FACT-F score of ≥3 points, whereas subjects with a FACT-F score change of < 3 points were considered to have stable fatigue (SF). There was no difference in fatigue between the IF (n = 20) and SF (n = 16) groups at baseline ($p = 0.69$). The IF subjects experienced significantly increased fatigue at the midpoint of EBRT compared to the SF subjects ($d = 1.65$, $p = 6.08 \times 10^{-7}$).

Fig. 2

Perception of cognitive capability was associated with fatigue during external-beam radiation therapy (EBRT). **a** Perceived cognitive impairment significantly increased in the IF (increased fatigue) subjects (n = 20) from baseline to the midpoint of EBRT ($d = 1.28$, $p = 6.71 \times 10^{-6}$). **b** Performance on the Stroop test under either the congruent or the incongruent condition was comparable between the IF (n = 20) and SF (stable fatigue) (n = 16) subjects ($p > 0.05$). rPFS, revised Piper Fatigue Scale.

Fig. 3

Memory impairment was associated with fatigue during external-beam radiation therapy (EBRT). **a** Screenshot of the virtual reality environment in CAMCI® (image credit: Psychology Software Tools, Inc.). **b** In the route finding task, the subject was provided with directions to the grocery store at the beginning of the shopping trip, and the directions remained on the screen throughout the shopping trip. The subject was asked to choose the direction to go at each intersection, and the *y* axis indicates percent accuracy. The IF (increased fatigue) subjects ($n = 20$) exhibited impaired executive function and decision-making in the route finding task compared to the SF (stable fatigue) subjects ($n = 16$) at the midpoint of EBRT ($d = 0.86$, $p = 0.04$). **c** In the item recall task, the subject was shown a list of items to purchase at the grocery store. At the end of the shopping trip, the subject was asked to select images of the items that needed to be purchased. The IF subjects ($n = 20$) exhibited impaired functional memory accuracy compared to the SF subjects ($n = 16$) at the midpoint of EBRT ($d = 1.07$, $p = 0.02$). **d** In the word recognition task, the subjects were instructed to select words they had previously encountered in the learning phase. Fatigue significantly correlated with speed ($r = 0.46$, $p = 0.009$) but not accuracy in the word recognition task. FACT-F, Functional Assessment of Cancer Therapy – Fatigue.

Fig. 4

Longitudinal learning effect of various CAMCI® tasks. Performance on each CAMCI® task is shown as the percentage of correct answers. Each line indicates the average score on each CAMCI® task for all subjects. Overall, the subjects improved on the majority of the CAMCI® tasks over the three time points tested (baseline, midpoint of EBRT, and EBRT completion). $F(2, 22) = 8.13$, $p = 0.002$.

Table 1

Demographics and clinical characteristics of the sample population

	Total (*n* = 36)	**Increased fatigue (*n* = 20)**	**Stable fatigue (*n* = 16)**	***p* value**
Age, years	66.50±1.17	67.30±1.43	65.63±1.98	0.49
BMI	30.07±0.73	30.63±1.09	28.88±0.86	0.23
Race				0.12
Asian	5.56%	5%	6.25%	
Black	27.78%	25%	31.25%	
Hispanic	2.78%	0%	6.25%	
White	63.89%	70%	56.25%	
Education				0.18
9th–12th, not a graduate	8.33%	15%	6.25%	
High school graduate/GED	5.56%	0%	12.5%	
Associate degree/some college	5.56%	10%	0%	
Bachelor's degree	36.11%	50%	18.75%	
Advanced degree	25.00%	15%	31.25%	
No answer	19.44%	10%	31.25%	
T stage				0.26
1c	25.00%	35%	18.75%	
2a	30.56%	15%	43.75%	
2b	2.78%	5%	0%	
2c	16.67%	25%	31.25%	
3	11.11%	20%	6.25%	
Gleason score				0.36
6	8.33%	10%	6.25%	
7	41.67%	45%	43.75%	
8	30.56%	20%	43.75%	
9	16.67%	25%	6.25%	
ADT use	75%	85%	62.5%	0.02
PSA at baseline, ng/mL	10.21±5.08	10.21±5.08	5.69±1.63	0.46
PSA at completion of EBRT, ng/mL	0.47±0.26	0.47±0.26	0.60±0.29	0.74

BMI, body mass index; GED, general equivalency diploma; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; EBRT, external-beam radiation therapy.

Table 2

Skills and health status of the sample based on CAMCI® responses

	Total (*n* = 36)	**Increased fatigue (*n* = 20)**	**Stable fatigue (*n* = 16)**
Is currently driving	97%	97%	97%
Has ever driven	100%	100%	100%
Has ever used a computer	94%	94%	94%
Has ever used an ATM	79%	79%	79%
Anxiety			
At baseline	18%	15%	19%
At midpoint of EBRT	13%	20%	0%
At endpoint of EBRT	16%	20%	6%
Alcohol use			
At baseline	3%	5%	0%
At midpoint of EBRT	0%	0%	0%
At endpoint of EBRT	0%	0%	0%
Depression			
At baseline	9%	5%	12%
At midpoint of EBRT	3%	5%	0%
At endpoint of EBRT	6%	10%	0%

CAMCI®, Computer Assessment of Mild Cognitive Impairment; ATM, automated teller machine; EBRT, external-beam radiation therapy.