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Survivorship: Cognitive Function, Version 1.2014:

Clinical Practice Guidelines in Oncology

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Abstract

Cognitive impairment is a common complaint among cancer survivors and may be a consequence of the tumors themselves or direct effects of cancer-related treatment (eg, chemotherapy, endocrine therapy, radiation). For some survivors, symptoms persist over the long term and, when more severe, can impact quality of life and function. This section of the NCCN Guidelines for Survivorship provides assessment, evaluation, and management recommendations for cognitive dysfunction in survivors. Nonpharmacologic interventions (eg, instruction in coping strategies; management of distress, pain, sleep disturbances, and fatigue; occupational therapy) are recommended, with pharmacologic interventions as a last line of therapy in survivors for whom other interventions have been insufficient.

Cognitive impairment is a common complaint among cancer survivors and may be a consequence of the tumors themselves or direct effects of cancer-related treatment (eg, radiation therapy). This symptom may be especially prominent in survivors of primary central nervous system (CNS) cancers or those with brain metastases. In addition, survivors who never had brain involvement may also report difficulties in cognition.[1] For some survivors, symptoms persist over the long term.[2] When more severe, the presence of cognitive dysfunction can impact quality of life and function. Cognitive dysfunction is most commonly connected with chemotherapy (sometimes referred to as "chemobrain"), but evidence suggests that therapies other than chemotherapy, such as endocrine therapy and radiation, may be associated with cognitive impairments.[3–9] A recent national cross-sectional study found that a history of cancer is independently associated with a 40% increase of the likelihood of self-reported memory problems.[10]

Cancer-related cognitive changes have primarily been studied in patients with CNS and breast cancers and lymphoma, and those who have undergone hematopoietic stem cell transplant (HSCT), with a wide incidence ranging from 19% to 78%.[2,11–24] Deficits

commonly occur in the domains of executive function, learning and memory, attention, and

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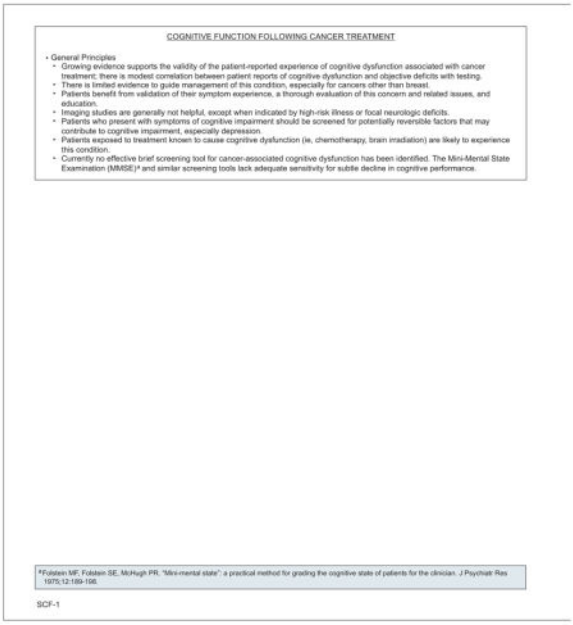
processing speed.[2,23]

Growing evidence supports the patient experience of cognitive dysfunction associated with cancer and its treatment. In one meta-analysis of 17 studies, women treated with chemotherapy for breast cancer 6 or more months previously (n=807) had lower functional abilities than those not treated with chemotherapy (n=291).[14] These deficits were limited to verbal (eg, word-finding) and visuospatial (eg, copying complex images) abilities. However, when compared with their prechemotherapy baseline, no differences were noted among patients complaining of cognitive dysfunction. In another study, cognitive function was compared among 196 long-term survivors of breast cancer treated with cyclophosphamide, methotrexate, and fluorouracil (CMF) who were, on average, 21 years out from diagnosis, and 1509 control patients with no history of cancer.[25] The chemotherapy group did significantly worse on several neuropsychological tests (eg, immediate and delayed verbal memory, executive functioning, psychomotor speed). Finally, one study compared 101 patients who underwent an HSCT with 82 patients treated with a nonmyeloablative therapy; both groups showed mild cognitive impairments at baseline.[26] Although no significant differences in cognitive dysfunction were identified at 2-year follow-up, patients who underwent HSCT had poorer performances in several areas, including attention and executive and psychomotor functions.


COGNITIVE FUNCTION FOLLOWING CANCER TREATMENT

• General Principles
- Growing evidence supports the validity of the patient-reported experience of cognitive dysfunction associated with cancer treatment; there is modest correlation between patient reports of cognitive dysfunction and objective deficits with testing.
- There is limited evidence to guide management of this condition, especially for cancers other than breast.
- Patients benefit from validation of their symptom experience, a thorough evaluation of this concern and related issues, and education.
- Imaging studies are generally not helpful, except when indicated by high-risk illness or focal neurologic deficits.
- Patients who present with symptoms of cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment, especially depression.
- Patients exposed to treatment known to cause cognitive dysfunction (ie, chemotherapy, brain irradiation) are likely to experience this condition.
- Currently no effective brief screening tool for cancer-associated cognitive dysfunction has been identified. The Mini-Mental State Examination (MMSE)* and similar screening tools lack adequate sensitivity for subtle decline in cognitive performance.

*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.

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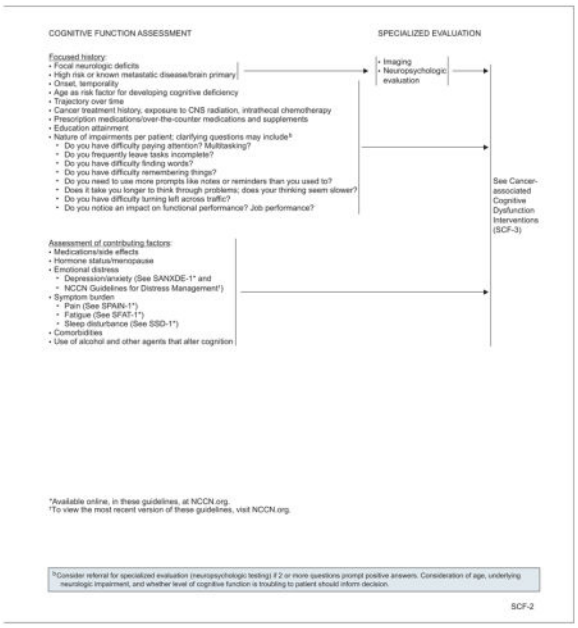

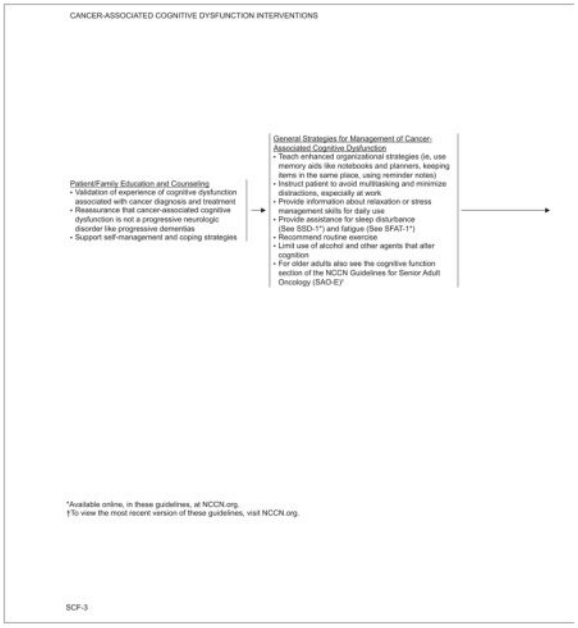

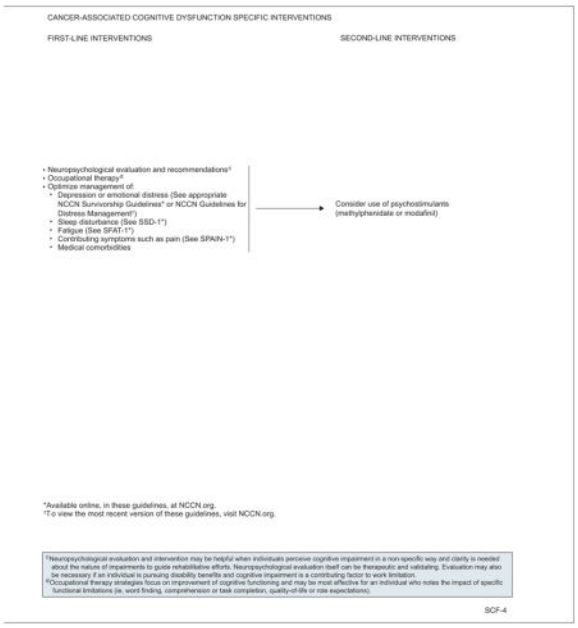

The correlation between patient reports of cognitive decline and results of neuropsychological testing has not been consistently demonstrated, possibly because of various definitions of cognitive dysfunction and differences in the statistical analyses across studies.[23] However, a recent study of 189 breast cancer survivors found that memory and executive function complaints, present in approximately 20% of the cohort, showed a statistically significant association with results of domain-specific neuropsychological tests.[27]

The underlying mechanisms that might increase the risk for chemotherapy-induced cognitive changes are not known. Studies have reported elevated levels of cytokines or DNA damage as some of the possible mechanisms.[28] Structural studies have supported the hypothesis that neurotoxicity resulting in damage to white matter of the brain may play an important role in cognitive deficits after chemotherapy treatment.[2,5,13,29,30] In addition, fatigue and depression, common in cancer survivors, may negatively influence cognitive function, although several studies have found that cognitive dysfunction does not correlate with mood.[25,31] Psychosomatic effects can also contribute, as evidenced by a recent study of patients to be treated with chemotherapy, which found that those who were informed of the possible cognitive side effects were more likely to report cognitive dysfunction and perform worse on neuropsychological testing than uninformed patients.[32] A better understanding of the mechanisms that cause cancer-related cognitive impairment is essential for the development of treatments to improve cognitive function and quality of life in patients with cancer and survivors.[1,33,34]

In October 2006, the International Cognition and Cancer Taskforce (ICCTF) was formed, comprising a multidisciplinary group of health professionals and health advocates. The mission of ICCTF is to advance understanding of the impact of treatment-related cognitive and behavioral functioning in patients with non-CNS cancers.[35] The group recently published recommendations regarding neuropsychological testing, defining cognitive

impairment/changes, and future study design.[34] ICCTF also has a Web site (www.icctf.com) to provide up-to-date information to both physicians and patients seeking assistance in the management of cognitive symptoms associated with cancer treatment.

Assessment and Evaluation for Cognitive Dysfunction

Patients who present with symptoms of cognitive impairment should be screened for potentially reversible factors that may contribute to cognitive impairment, including depression, pain, fatigue, and sleep disturbance. Some medications can also contribute to cognitive impairment. Therefore, current medications, including over-the-counter medications and supplements, should be reviewed. Any potentially contributing factor should be addressed.

For those who present with concomitant focal neurologic deficits and those whose symptoms evolve to include these findings, imaging is indicated to rule out brain or CNS disease. In addition, imaging in the absence of focal findings may be appropriate for patients deemed to be at high risk for recurrence or metastatic disease involving the CNS.

Unfortunately, no effective brief screening tool currently exists for cancer-associated cognitive dysfunction in the asymptomatic cancer survivor. The Mini-Mental State Examination (MMSE[36]) and similar screening tools lack adequate sensitivity to detect a subtle decline in cognitive performance. Instead, the panel listed several questions that can help clarify the nature of the impairment, including inquiries about the ability to pay attention, find words, remember things, think clearly, and perform functions. The time of onset and the trajectory over time should also be assessed.

Neuropsychological evaluation may be helpful when individuals perceive cognitive impairment in a nonspecific way and clarity is needed about the nature of impairments to guide rehabilitative efforts. Neuropsychological evaluation itself can be therapeutic and validating. Evaluation may also be necessary if an individual is pursuing disability benefits and cognitive impairment is a contributing factor to work limitation.

Management of Cognitive Dysfunction

Survivors benefit from validation of their symptom experience and should be reassured that, in most patients, cognitive dysfunction does not worsen over time. In fact, data from breast cancer survivors suggest that symptoms may improve over time.[4] The panel recommends the use of nonpharmacologic interventions whenever possible, with pharmacologic interventions as a last line of therapy in survivors for whom other interventions have been insufficient, as discussed in the following sections. Additional recommendations for cognitive dysfunction in older adults can be found in the cognitive function section of the NCCN Guidelines for Senior Adult Oncology (to view the most recent version of these guidelines, visit NCCN.org).

Nonpharmacologic Interventions for Cognitive Dysfunction

Prospective data are lacking to inform the use or potential benefits of nonpharmacologic interventions for cancer survivors who complain of cognitive dysfunction. In one small

study, cognitive behavioral therapy was evaluated in 40 breast cancer survivors using a waitlist control trial design.[37] Although overall quality of life improved with the intervention, statistically significant improvement was noted only with verbal memory, not with self-reports of daily cognitive complaints.

Practical suggestions include instruction in self-management and coping strategies (eg, using planners and reminder notes, keeping items in the same place, minimizing distractions, avoiding multitasking), which the panel believes can be very helpful to patients. Discontinuation or limitation of use of medications known to cause or contribute to cognitive impairment should be attempted. Management of distress, pain, sleep disturbances, and fatigue should be provided. In fact, a recent study showed that cognitive behavioral therapy for fatigue was effective at reducing self-reported cognitive disability and concentration problems in 98 severely fatigued cancer survivors.[38] Finally, relaxation, stress management, and routine exercise should all be encouraged. Substantial evidence shows that physical activity enhances cognitive function in elderly people in general, although only few studies specific to cancer survivors have been reported.[39–41]

Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for individuals who note the impact of specific functional limitations, such as word finding, comprehension, task completion, work performance, quality of life, or role expectations.[42]

Pharmacologic Interventions for Cognitive Dysfunction

If nonpharmacologic interventions have been insufficient, consideration of psychostimulants such as methylphenidate or modafinil is reasonable, although data informing the efficacy of these agents are lacking. Trials assessing the effects of methylphenidate have reported mixed results.[43] For example, a randomized, placebo-controlled, double-blind trial found that d-methylphenidate had no effect on neuropsychological test scores.[44] In contrast, a randomized, double-blind, crossover trial of child survivors of acute lymphoblastic leukemia or brain tumors showed that methylphenidate was more effective than placebo at improving attention, cognitive flexibility, and processing speed.[45]

Results of studies on modafinil are more consistent. A randomized controlled trial assessing the efficacy of modafinil for fatigue and cognitive function in breast cancer survivors found significantly greater improvement in memory and attention among patients receiving modafinil than in the placebo group.[46] Similarly, a double-blind, randomized, crossover trial also in breast cancer survivors found that participants receiving modafinil performed significantly better on cognitive tests of attention and psychomotor speed.[47] Benefits with treatment were also noted among patients with a primary brain tumor.[48]

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