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. 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. (J Natl Compr Canc Netw 2014;12:976–986)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. The full NCCN Guidelines for Survivorship are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Survivorship Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Survivorship Panel members can be found on page 986. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
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 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 survi

Text cont. on page 982.
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 (i.e., 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.

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SCF-1


COGNITIVE FUNCTION ASSESSMENT

Focused history:
- Focal neurologic deficits
- High risk or known metastatic disease/brain primary
- Onset, temporality
- Age as risk factor for developing cognitive deficiency
- Trajectory over time
- Cancer treatment history, exposure to CNS radiation, intrathecal chemotherapy
- Prescription medications/over-the-counter medications and supplements
- Education attainment
- Nature of impairments per patient; clarifying questions may include\(^b\):
  - Do you have difficulty paying attention? Multitasking?
  - Do you frequently leave tasks incomplete?
  - Do you have difficulty finding words?
  - Do you have difficulty remembering things?
  - Do you need to use more prompts like notes or reminders than you used to?
  - Does it take you longer to think through problems; does your thinking seem slower?
  - Do you have difficulty turning left across traffic?
  - Do you notice an impact on functional performance? Job performance?

Assessment of contributing factors:
- Medications/side effects
- Hormone status/ menopause
- Emotional distress
  - Depression/anxiety (See SANXDE-1* and NCCN Guidelines for Distress Management\(^t\))
- Symptom burden
  - Pain (See SPAIN-1*)
  - Fatigue (See SFAT-1*)
  - Sleep disturbance (See SSD-1*)
- Comorbidities
- Use of alcohol and other agents that alter cognition

SPECIALIZED EVALUATION

- Imaging
- Neuropsychologic evaluation

See Cancer-associated Cognitive Dysfunction Interventions (SCF-3)

\(^b\)Consider referral for specialized evaluation (neuropsychologic testing) if 2 or more questions prompt positive answers. Consideration of age, underlying neurologic impairment, and whether level of cognitive function is troubling to patient should inform decision.

\(^t\)To view the most recent version of these guidelines, visit NCCN.org.

*Available online, in these guidelines, at NCCN.org.
CANCER-ASSOCIATED COGNITIVE DYSFUNCTION INTERVENTIONS

**Patient/Family Education and Counseling**
- Validation of experience of cognitive dysfunction associated with cancer diagnosis and treatment
- Reassurance that cancer-associated cognitive dysfunction is not a progressive neurologic disorder like progressive dementias
- Support self-management and coping strategies

**General Strategies for Management of Cancer-Associated Cognitive Dysfunction**
- Teach enhanced organizational strategies (i.e., use memory aids like notebooks and planners, keeping items in the same place, using reminder notes)
- Instruct patient to avoid multitasking and minimize distractions, especially at work
- Provide information about relaxation or stress management skills for daily use
- Provide assistance for sleep disturbance (See SSD-1*) and fatigue (See SFAT-1*)
- Recommend routine exercise
- Limit use of alcohol and other agents that alter cognition
- For older adults also see the cognitive function section of the NCCN Guidelines for Senior Adult Oncology (SAO-E)*

*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

SCF-3
CANCER-ASSOCIATED COGNITIVE DYSFUNCTION SPECIFIC INTERVENTIONS

FIRST-LINE INTERVENTIONS

- Neuropsychological evaluation and recommendations
- Occupational therapy
- Optimize management of:
  - Depression or emotional distress (See appropriate NCCN Survivorship Guidelines* or NCCN Guidelines for Distress Management
  - Sleep disturbance (See SSD-1*)
  - Fatigue (See SFAT-1*)
  - Contributing symptoms such as pain (See SPAIN-1*)
  - Medical comorbidities

SECOND-LINE INTERVENTIONS

- Consider use of psychostimulants (methylphenidate or modafinil)

*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

Neuropsychological evaluation and intervention may be helpful when individuals perceive cognitive impairment in a non-specific 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.

Occupational therapy strategies focus on improvement of cognitive functioning and may be most effective for an individual who notes the impact of specific functional limitations (ie, word finding, comprehension or task completion, quality-of-life or role expectations).
Survivorship, Version 1.2014

Text cont. from page 977.

vors 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. 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. 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.

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. 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.

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. 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. 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. 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. 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.

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. The group recently published recommendations regarding neuropsychological testing, defining cognitive impairment/changes, and future study design. 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) 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
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{43} For example, a randomized, placebo-controlled, double-blind trial found that d-methylphenidate had no effect on neuropsychological test scores.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{47} Benefits with treatment were also noted among patients with a primary brain tumor.\textsuperscript{48}

**References**

34. Goedendorp MM, Knoop H, Gielissen MF, et al. The effects of cognitive behavioral therapy for postcancer fatigue on perceived...


## Individual Disclosures for the NCCN Survivorship Panel

<table>
<thead>
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