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REVIEW ARTICLE

Cancer-related cognitive impairment in patients with non-central nervous system malignancies: an overview for oncology providers from the MASCC Neurological Complications Study Group

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Abstract

Cancer-related cognitive impairment (CRCI) is commonly experienced by individuals with non-central nervous system cancers throughout the disease and treatment trajectory. CRCI can have a substantial impact on the functional ability and quality of life of patients and their families. To mitigate the impact, oncology providers must know how to identify, assess, and educate patients and caregivers. The objective of this review is to provide oncology clinicians with an overview of CRCI in the context of adults with non-central nervous system cancers, with a particular focus on current approaches in its identification, assessment, and management.

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Cognitive impairment is commonly experienced by people with cancer throughout the disease trajectory [1]. Whether this impairment stems from underlying cancer or its treatment, it can have a substantial impact on the functional ability and quality of life of patients and their families [2–7]. To mitigate the impact, oncology providers must know how to identify, assess, and educate patients and caregivers. This review aims to provide oncology clinicians with an overview of non-central nervous system (CNS) cancer-related cognitive impairment (CRCI) as it pertains to adults, including current approaches in its identification, assessment, and management. We focus our discussion on non-CNS cancer, where the basic mechanism of cognitive impairment does not stem directly from cancer located within the CNS.

Scope of problem

The term Cancer-Related Cognitive Impairment (CRCI), sometimes referred to as "chemo brain" by patients, is commonly used to refer to the cognitive problems associated with cancer and cancer treatments experienced by individuals with cancer. It often involves problems with memory, attention/concentration, processing speed, and executive functions [8]. While much research has focused on breast cancer, CRCI affects patients across a wide range of non-CNS solid tumor and hematological cancers [9–12]. An estimated 30–40% of people with cancer exhibit some form of cognitive impairment before chemotherapy, an additional 50–75% may exhibit impairment during chemotherapy, and approximately 35% of survivors continue to show impairment in the months to years after treatment completion [13]. However, long-term data is limited.

While CRCI experienced during treatment is likely to subside over time, many will have persistent difficulties resulting in long-term challenges. In a recent survey of 3108 cancer survivors who were, on average, 4.6 years post-diagnosis, nearly half (45.7%) reported some cognitive impairment [14]. Prevalence was similar among respondents across a range of non-CNS cancers, with about half of study participants with breast, lymphoma, colorectal, and head and neck cancers reporting CRCI (44.2–57.6%) [14]. Given that cognitive difficulties may interfere with the fulfillment of personal and work-related responsibilities [2, 3], emotional and social well-being [5, 6], and instrumental activities of daily living [7], there is a need for healthcare providers to assess and manage CRCI.

Clinical presentation of CRCI in people with non-CNS malignancies

Throughout their cancer trajectory, people may develop the signs and symptoms of CRCI [1], ranging from mild forgetfulness or trouble focusing to frank cognitive difficulties (see Table 1). Generally speaking, cognitive deficits in CRCI align with a frontal-subcortical presentation, in which deficits are subtle and variable [15]. Moreover, these symptoms can fluctuate, depending on the patient's condition. Sometimes symptoms of CRCI become more apparent when patients are fatigued, stressed, lack sleep, have a metabolic derangement, and have mood dysfunction [16].

Factors contributing to CRCI

A multitude of factors appears to be associated with CRCI, including underlying cancer, treatment modalities, and other individual patient-related factors (Fig. 1). While the biological underpinning of CRCI remains under investigation, putative mechanisms relate to the neuroimmunological pathways. A recently published review summarizes pre-clinical and clinical data supporting these hypotheses [17].

Underlying cancer

Studies have shown that CRCI is present before the commencement of systemic treatment for non-CNS cancers, including breast [18], colorectal [19], testicular [20], head and neck [21], and hematological [22] cancers, suggesting that cancer itself may contribute to CRCI. However, there are likely differences between localized/metastatic and solid/hematological cancers.

Table 1 Common signs and symptoms of cancer-related cognitive impairment

- Difficulties with multitasking, attention, following instructions, completing complex tasks, and concentration
- Amotivation or decreased motivation
- Anhedonia
- Difficulties with naming familiar objects and people
- Changes in behavior and temperament
- Difficulties with visuospatial tasks
- Changes in mood and personality
- Frank memory loss (usually anterograde rather than retrograde)

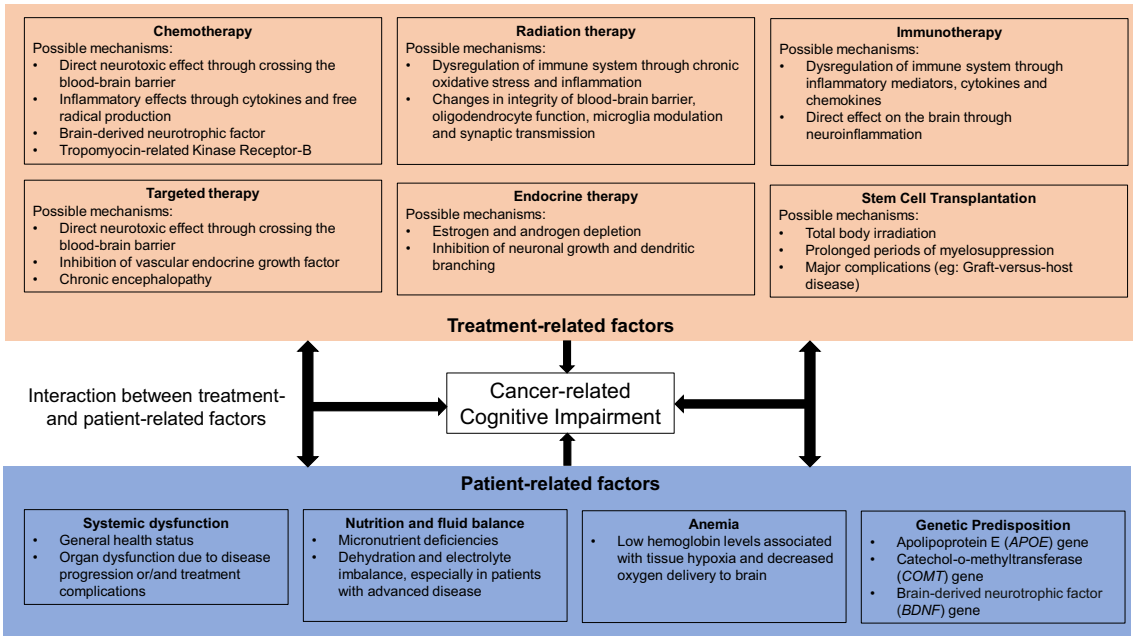

Fig. 1 Contributing factors of cancer-related cognitive impairment

Investigators have theorized that peripheral inflammatory cytokines stimulate inflammation in the brain, resulting in neuronal dysfunction and abnormal neurotransmitter activity important for supporting cognitive function. Neuroimaging data show reductions in white matter volume in breast cancer patients, even before exposure to chemotherapy, and compared with age-matched female controls [23].

Treatment-related factors

Chemotherapy Numerous meta-analyses demonstrate the association between chemotherapy and CRCI [24–26]. In a nationwide US study, worsening self-reported cognitive function was reported in patients with breast cancer from pre- to post-chemotherapy as compared to healthy non-cancer controls. Furthermore, cognitive impairment persisted at 6-months post-chemotherapy and was worse at all time-points from pre- to post-treatment [27, 28]. Even 10 years after chemotherapy treatment, MRI imaging confirms decreased network connectivity in the frontal, striatal, and temporal regions in patients compared to healthy controls [29].

There are several ways chemotherapeutic agents may impact cognitive functioning. For example, taxane administration is associated with elevated levels of cytokines, such as interleukin (IL)-6, IL-8, and IL-10, which in turn lead to neurotoxicity, alterations of glial cells, and reductions in neural repair [30]. DNA damage resulting from direct inflammatory effects, oxidative stress, and increased free radical formation also plays essential roles in the impairment cascade [31]. Both white matter and gray matter loss has been observed primarily in the frontal lobes and hippocampus, which may explain some memory and behavioral changes noted [32]. Preclinical models suggest that methotrexate disrupts brain-derived neurotrophic factor (BDNF) and tropomyocin-related kinase receptor-B (TrkB) signaling in oligodendrocyte precursor cells necessary for myelination mediated by inflammatory microglia [33, 34]. Determining the impact of individual agents on CRCI is complicated by the ubiquity of chemotherapeutic combinations and methodological heterogeneity across studies.

Radiation therapy Cognitive impairment can also develop in patients with cancers that require treatment with radiation therapy [35]. Patients most likely affected include primary brain tumor patients, patients with metastatic disease to the brain, patients with head and neck cancers, and patients that undergo prophylaxis cranial irradiation or craniospinal radiation. It is well documented that radiation therapy can cause brain injury and hence cognitive dysfunction. Although pathophysiologic mechanisms are not completely elucidated [36], several theories explain radiation therapy-associated brain injury. First, activation of the immune system after radiation therapy, initially protective, can cause chronic oxidative stress and inflammation, leading to neuronal damage and resulting in cognitive impairment [37]. Vascular and parenchymal hypotheses explain brain injury after irradiation by mechanisms that include changes in blood-brain barrier (BBB), ischemia, oligodendrocyte function, microglia modulation, synaptic transmission, secretion of neurotrophic factors, signaling between astrocytes and endothelial cells, and complex interactions among various elements in the microenvironment [38].

Immunotherapy In recent years, checkpoint inhibitors have become an important treatment modality for many cancers [39]. Central immune activation via checkpoint inhibitors may lead to consequent neuroinflammation, increasing pro-inflammatory mediators, cytokines, and chemokines; all of this is more prominent when used in combination treatments with radiation therapy or multiple immunotherapy agents [40, 41]. In a phase 2 trial of pembrolizumab in patients with CNS metastases for melanoma or non-small cell lung cancer, two of the 32 patients showed cognitive impairment, one of which had a severe event that resulted in study withdrawal [42]. Further research to understand the cognitive effects of checkpoint inhibitors in the absence of CNS involvement is needed. The emergence of chimeric antigen receptor (CAR) T cell therapy as a novel immunotherapy for hematological and some solid tumors further highlights the potential impact of immune activation on cognitive function. The cytokine release associated with CAR T cell therapy has been implicated in the significant acute neurotoxicity in approximately 30% of patients, characterized by aphasia, delirium, and sometimes coma that appears to be mostly reversible, but the long-term cognitive effects are unknown. As summarized in a recent review [43], the role of immunotherapies on the development of CRCI requires further prospective research, including the long-term implications from the "cytokine storm" often associated with immunotherapy use.

Targeted therapies Targeted therapy agents, such as monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs), are one of the primary treatments for the management of a host of malignancies. Vascular endothelial growth factor (VEGF) is a signaling protein thought to be involved in synaptic plasticity and in the setting of glioblastoma, VEGF-inhibition with bevacizumab has been associated with objective global cognitive decline [44, 45]. However, in breast cancer patients receiving chemotherapy, changes in plasma VEGF levels during anthracycline treatment were not associated with CRCI [46]. In the non-CNS context, there are limited data regarding the short-term cognitive impact of TKIs for a subset of agents. One study investigated cognitive function in people with metastatic renal cell carcinoma or gastrointestinal stromal tumor (GIST) receiving treatment with the multi-kinase inhibitors, sorafenib or sunitinib. The authors reported significant impairment in learning and memory domains, as well as in executive function, in these patients when compared to healthy controls [47]. The dose-limiting toxicity of proteasome inhibitors is classical peripheral neuropathy, but there is a recent report of chronic encephalopathy in some multiple myeloma patients exposed to proteasome inhibitors [48]. The long-term neurologic sequelae of targeted therapies have not been studied.

Endocrine therapy Breast and prostate cancer survivors are treated most frequently with endocrine therapies, classes of agents that include aromatase inhibitors, tamoxifen, and GnRH agonists [49]. Estrogen and associated hormones are essential in cognitive function, neuroprotection, and neuroplasticity. It has been suggested that estrogen can act on membrane receptors to activate intracellular signaling mechanisms, which exerts neurotrophic effects found in brain areas essential for learning and memory. Estrogen receptors were found to be expressed in the hippocampus and the frontal cortex [50, 51]. Compared to healthy controls, women treated with endocrine therapies demonstrate poorer verbal and visual learning, even in the absence of prior chemotherapy [52–54] and can be more severe in older survivors [55]. However, longitudinal differences in cognitive functioning between women treated with or without endocrine therapy for early-stage breast cancer were not found over 6 years [56]. Estradiol decline was also reported to be associated with cognitive domains of verbal fluency and visual memory in men with prostate carcinoma undergoing androgen deprivation [57]. The potential for cognitive changes in the context of androgen deprivation in the treatment of prostate cancer is an active area of research [12].

Hematopoietic stem cell transplantation Stem cell transplantation is a potentially curative treatment for a range of hematological malignancies. This treatment is an intensive systemic modality involving high-dose chemotherapy, sometimes with total body irradiation, prolonged periods of myelosuppression, immunosuppressive therapies, and major complications, such as graft-versus-host disease. Despite longitudinal studies indicating that, on average, cognitive functioning should be expected to recover to pre-transplant levels over time [10, 58, 59], persistent impairment has been observed in a subgroup of patients up to 5 years after treatment [59], particularly those treated with allogeneic (vs. autologous) stem cell transplant [58].

Cancer surgery Surgery is an important modality for treatment of solid tumors. Studies on patients with breast cancer have demonstrated that even before the initiation of chemotherapy, surgery may be associated with an elevated stress level that leads to cognitive impairment [60, 61]. The mediating effect of stress on cognitive outcomes may be more apparent in patients with less effective coping strategies [60]. In particular, elderly patients with cancer may be more sensitive to the cognitive effects of surgery and types of anesthesia used due to inflammatory factors and stress response [62].

Patient-related factors

Systemic dysfunction Co-morbidities that pre-exist or develop during cancer treatment may impact cognitive functioning. In older breast cancer patients, diabetes and cardiovascular disease were associated with greater pre-treatment cognitive impairment in patients but not controls [63]. There is some evidence that those with more co-morbidities after treatment may experience slower recovery of cognitive function [64, 65].

In non-cancer settings, cognitive impairment, affecting memory, concentration, and psychomotor functions, is associated with renal disease and liver failure [66–68]. The role of micronutrients, such as vitamin D, water-soluble vitamins B and C, and minerals (calcium, magnesium, and zinc), on cognitive performance is also well-established [69–71]. Malnutrition, dehydration, and electrolyte imbalances can occur as a result of advanced disease and treatment complications [72, 73].

A small study in elderly patients undergoing chemotherapy for lung cancer showed that chemotherapy-induced anemia was associated with cognitive impairment [74]. Studies investigating the effect of erythropoietin administration to treat anemia in cancer patients on cognition, however, have resulted in conflicting results, with some studies showing benefit [74, 75], while others have not [76, 77]. Given the risk of potential adverse cardiovascular effects and increased tumor growth related to the use of erythropoietin for cancer patients, it is not recommended as a treatment of CRCI [78]

Genetic predisposition Several studies have investigated how genetic polymorphisms impact the risk of cognitive changes in patients receiving chemotherapy. These genes include the apolipoprotein E (*APOE*) gene, the catechol-o-methyltransferase (*COMT*) gene, the brain-derived neurotrophic factor (*BDNF*) gene, and pro-inflammatory cytokine (IL-6 and TNF-α) genes. One research group reported that in breast cancer and lymphoma survivors carrying the ε4 allele of the *APOE* gene, there was an association more likely to have cognitive problems in the domains of visual memory, spatial ability, and psychomotor functioning [79]. In older breast cancer survivors, the same genotype was associated with longitudinal decreases in cognitive functioning over 24 months from diagnosis [80]. Similarly, testicular cancer patients who were carriers of the ε4 allele of the *APOE* gene experienced poorer overall cognitive performance [81]. Interestingly, this association between the ε4 allele of the *APOE* and CRCI was not observed in a cohort of colorectal cancer patients [19]. Two research studies have shown that single-nucleotide polymorphisms of the *COMT* gene were associated with CRCI in breast cancer patients [82, 83]. In contrast, in an Asian breast cancer cohort, individuals with the *BDNF* gene polymorphism (Val66Met) properties were less likely to report CRCI after chemotherapy [84, 85]. DNA methyltransferases, which affect methylation and epigenetic processes, have also been found to contribute to CRCI [86].

Screening for CRCI

Identifying individuals with CRCI is necessary to ensure adequate supportive care is provided to those who need it. As a first step, the integration of cognitive issues in routine symptom screening can normalize cognitive issues as a part of standard cancer care. For example, the US-based National Comprehensive Cancer Network (NCCN) Distress Thermometer and Problem List has been adopted in clinical settings to help identify the needs of people with cancer across a range of areas and includes one item regarding cognitive functioning [87, 88]. The NCCN suggests the use of probing questions (Table 2) [89] that can be integrated into routine symptom assessment during clinical encounters to facilitate the identification of patients with cognitive issues.

Patient-reported outcome measures Standardized patient-reported outcome measures (PROM) aimed specifically at identifying cognitive concerns provide information regarding the nature of patients' subjective experiences of cognitive deficits, to guide decision-making regarding the need for further psychological assessment and intervention. One commonly used self-reported measure, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)-Cognitive Functioning Scale [90], is comprised of two brief items to assess perceived difficulty in memory and attention with recently published thresholds of clinical importance [91]. The Functional Assessment of Cancer Therapy-Cognition (FACT-Cog version 3) [92] is also widely used; scoring of its 37 items results in total and domain scores, including a domain that captures the impact of cognitive difficulty on individuals' quality of life. Selection of an appropriate PROM may depend on several factors, including but not limited to: psychometric properties, recall period, time to completion, availability of normative comparison data, language translations, and clinically meaningful thresholds. A recent systematic review provides a summary of PROMs used in patients with cancer [93].

Objective screening tools While an objective screening tool for CRCI would be desirable, there is currently no gold standard for routine use in the clinical setting. For older adults with cancer, expert panels within organizations, such as the American Society of Clinical Oncology, recommend cognitive screening with tools such as the Mini-Cog or Blessed Orientation-Memory-Concentration Test as part of routine geriatric assessment [94]. Other options include the Mini-Mental State Examination (MMSE) [95] and the Montreal Cognitive Assessment (MoCA) [96]. However, as these measures were primarily to assess the risk of mild cognitive impairment or dementia, there is limited evidence to support their sensitivity as a screen for cognitive deficits characteristic of CRCI, particularly across the lifespan [97].

In-depth clinical assessment of CRCI

Once CRCI is suspected, further assessment may be indicated. A comprehensive clinical assessment of CRCI often requires referral to a neuropsychologist who directly conducts testing or who works with a trained administrator under their

Table 2 Examples of tools used in CRCI screening and assessment

	Examples
Probing Questions [89]	• Do you have difficulty paying attention/multi-tasking? • Do you have difficulty remembering things? • Does it take you longer to think through problems? • Does your thinking seem slower? • Do you notice an impact on functional performance? Job performance?
Patient-Reported Outcome Measures (PROM)	• European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)-Cognitive Functioning Scale • Functional Assessment of Cancer Therapy-Cognition (FACT-Cog version 3)
Cognitive Screening Tools (*sensitivity may be limited)	• Mini-Cog • Blessed Orientation-Memory-Concentration Test • Mini-Mental State Examination (MMSE) • Montreal Cognitive Assessment (MoCA)
Neuropsychological Tests	• Hopkins Verbal Learning Test-Revised (HVLT-R) • Trail Making Tests Parts A and B (TMT) • Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination. • Additional tests for working memory (e.g. Auditory Consonant Trigrams, the Paced Auditory Serial Addition Test (PASAT), Brief Test of Attention, WAIS-III Letter-Number Sequencing)

Licencing fees from developers may apply for these tools

guidance. The evaluation includes history taking and characterization of cognitive abilities, using neuropsychological testing and psychosocial assessments.

History taking

Providers should obtain a full history and physical examination to understand the underlying comorbidities that can augment cognitive impairment. Providers should ask about the time course of the symptoms, along with alleviating and mitigating factors. This includes an evaluation of all medications and supplements patients are taking, as they may be a causal factor in cognitive impairment. Engaging caregivers in the discussion of the patient's cognitive status can be helpful, as they may be the first to recognize cognitive changes and bring it to the attention of oncology providers [98].

If symptoms occur abruptly and then resolve quickly, providers should evaluate patients for seizures or CNS metastases with appropriate testing and neuro-imaging. Delirium should also be considered for patients with cognitive symptoms that occur abruptly, especially in patients with advanced cancer, as treatment for the cause may reverse the delirium, if related to opioid toxicity, infection, or dehydration [99, 100]. If focal neurological deficits, such as weakness to the face, arm, and leg on one side of the body or a visual field abnormality, are seen on neurological examination, one should promptly order appropriate neuro-imaging and diagnostic evaluation for brain metastases or other central neurological processes such as a cerebrovascular event. In non-CNS cancers, imaging techniques are not routinely used in the diagnosis of CRCI but hold promise in research (Supplement 2).

Older patients with cancer are at higher risk for cognitive impairment. This is likely due to the compounding effect of natural cognitive changes that occur with aging, which exerts the most significant impact on similar cognitive domains that show impairment in cancer, including memory, attention/concentration, and complex cognitive activities [101]. Cancer and its treatments have also been hypothesized to accentuate or accelerate aging in some patients [102, 103]. There is a higher prevalence of other cognitive disorders that can develop as one ages; these include mild cognitive impairment and Alzheimer's disease, multi-infarct dementia, and Parkinson's disease.

Neuropsychological assessment

Neuropsychological assessment is the most reliable method of identifying the breadth and severity of cognitive impairment and is especially useful in detecting mild cognitive changes [104, 105]. The development of an appropriate and clinically feasible approach for assessment and interpretation of results is best done in collaboration with a neuropsychologist. Still, the following is provided as an overview. The benefit of formal neuropsychological assessment is not only the reliable identification of cognitive changes, but also the ability for the trained clinician to provide feedback to the patient with relation to cognitive strengths and challenges, supported by strategies to limit the impact of deficits on functional ability.

The selection of an appropriate set of tests requires an understanding of the common impairments seen in CRCI using neuropsychological testing. Developed as a guide to harmonizing CRCI research studies, the International Cognition and Cancer Task Force (ICCTF) suggests prioritizing the use of

tests that evaluate the frontal subcortical profile, especially those that assess the domains of learning and memory, processing speed and executive function [106]. For English speakers, recommended tests are the Hopkins Verbal Learning Test-Revised (HVLT-R), the Trail Making Tests Parts A and B (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination. One can include additional tests to measure working memory, such as the Auditory Consonant Trigrams, the Paced Auditory Serial Addition Test (PASAT), the Brief Test of Attention, and the WAIS-III Letter-Number Sequencing [106] with the caveat that increasing the number of tests will lengthen testing duration, which may not be feasible in a clinical setting. Analysis includes a comparison of patients' performance to normative scores and/or monitored serially, to map the symptoms [106]. Age- and education-matched reference data should be used for comparison, if available, to differentiate CRCI from age-related cognitive deterioration and avoid confounding due to education level [107]. While abbreviated batteries are useful to cope with the time constraint, it is imperative to ensure that there are adequate reliability and correlation with the comprehensive battery [104]. Clinicians must strike a balance between a feasible testing duration and a thorough and comprehensive evaluation.

The two primary administration methods for neuropsychological testing are conventional paper-and-pencil tests and computerized assessments. Paper-and-pencil tests require extensive training before administration and scoring. Some tests also do not have alternate forms and are thus not suitable for serial assessments to monitor cognitive changes in patients over time. Computerized versions of neuropsychological tests often allow for greater control over test difficulty through manipulation of test parameters, including the presentation rate and complexity of stimuli, and alternate versions are often available to avoid practice effects if longitudinal monitoring of patients is required. Computerized tests may also reduce variability introduced by subject-interviewer interaction [104] and the need to travel to the clinical site, if remote testing is enabled [108]. Overall, decisions regarding administration method should balance feasibility with validity to provide a robust assessment of the cognitive domains of interest.

It is important to be aware that individuals with subjective cognitive complaints may not necessarily perform poorly on neuropsychological testing [105, 109]. Possible reasons include potential lack of sensitivity of chosen neuropsychological tests to detect subtle cognitive changes associated with cancer or lack of ecological validity of tests to domains affected. Neuropsychological assessments are also usually conducted under controlled conditions that likely differ from real-life challenges that patients face while carrying out daily activities. As a result, neuropsychological assessment may not wholly capture the impact of CRCI on daily activities and functioning of cancer patients. Subjectively measured cognition can also be impacted by other psychological factors, as people who report higher depressive symptoms are more likely to self-report cognitive impairment as compared to their performance on objective assessments [110], though meaningful change may still be present. The frequent co-occurrence of self-reported cognitive problems with depressive symptoms, fatigue, sleep disturbance, and pain appears to suggest a psychoneurological symptom cluster characterized by shared underlying mechanisms [111].

Management and treatment of CRCI

Patient education

The experience of cognitive difficulties can be distressing for patients and their caregivers, particularly when perceived as abnormal. Validation of cognitive concerns can help to normalize CRCI and facilitate individuals' coping [11, 112]. Though many individuals may adopt various adaptations to cognitive difficulties, ongoing provision of patient education and self-management support can help individuals' broaden their use of adaptive strategies [113]. Helpful adaptive strategies may include using organizational aids (e.g., lists, note-taking), finding activities to stay mentally stimulated, adjusting expectations, and seeking help when needed [6, 112]. Getting adequate rest and caring for mental health may also relieve cognitive symptoms. There is a range of resources for people with cancer and their caregivers, including support groups and societies, educational resources, and referral to key providers in the interprofessional team, including neuropsychology, social work, and occupational therapy.

Treatment interventions

The effective treatment of CRCI remains a clinical challenge, despite the growing number of studies evaluating various methods of treating CRCI. A range of interventions has been designed and tested to reduce self-reported cognitive symptoms and restore cognitive deficits. These interventions can be grouped broadly into cognitive training and rehabilitation, exercise, mind-body interventions, and pharmacotherapies and summarized below. Characteristics of clinical trials in each of these categories are presented in Tables 3 and 4.

Cognitive training and rehabilitation Cognitive training, which involves the use of repetitive, increasingly challenging tasks (often delivered via computer) to improve, maintain, or restore cognitive function, has been evaluated for the management of CRCI with mixed results [114–118]. One study reported improvements in objectively measured memory and speed of processing and perceived cognitive impairment

Table 3 Clinical trials of non-pharmacological interventions for CRCI in non-CNS cancers

Author, year, country	Study design, Number (*n*)	Population	Intervention summary	Outcomes	Notes
Cognitive Training					
Wu 2018 [119] USA	RCT *n* = 60 UC = 20 *I* = 40	Prostate cancer patients who had been on ADT ≥ 3 months	I: BrainHQ™ 1 h/day, 5 days/week for 8 weeks or 40 h total	50% recruitment rate, < 70% retention rate (when including non-completers). Improvement on reaction time ($p < 0.01$), but not on visual or verbal memory	Small sample Sample predominately White, married, well educated, with higher income Design – use of usual care vs. attention control Limited objective cognitive battery
Meneses 2018 [114] USA	RCT *n* = 57 *C* = 28 *I* = 29	Breast cancer survivors ≥ 21 years of age & ≥ 6 months post-primary treatment	C: No contact I: 2 h/week to complete 10 h over 6–8 weeks	Improvement in I compared to C	Small sample No contact control used vs attention control Did not control for age and education in analyses
Bray 2016 [117] Australia	RCT *n* = 242	Cancer survivors 6–60 months post-adjuvant chemotherapy; Self-reporting cognitive symptoms	C: One telephone consultation to teach compensatory strategies I: 15-week computer-based cognitive training 4 × 40 min/session per week + C	Cognitive symptoms significantly improved post-intervention ($p <$ .001) and 6 months later ($p <$ .001). No difference in neuropsychological performance.	Population largely women with breast cancer Low intervention completion rate Non-attention control group.
Damholdt 2016 [115] Denmark	RCT n = 157 C = 63 I = 94	Breast cancer survivors; Self-reporting cognitive symptoms	C: Wait list I: computerized training 30 sessions over 6 weeks	No improvement in self-report cognitive functioning	No attention control
Kesler 2013 [116] USA	RCT *n* = 41 *C* = 20 *I* = 21	Breast cancer survivors, aged at least 40 years, ≥ 1.5 years post-adjuvant chemotherapy	C: Wait list I: 48 session online Executive Function cognitive training program 20–30-min duration (5 exercises 4 times/week for 12 weeks)	Improvement in I compared to C: EF ES 0.58, p = .008. Verbal fluency ES 0.82, p = .003. Information processing ES 0.87 p = .009. BRIEF scores were not different ES 0.26, p = .22.	Very small sample size with multiple comparisons Some variability across neuropsychological tests WLC comparator group used while attention control would have been optimal
Von Ah 2012 [118] USA	RCT *n* = 88 *C* = 29 Ia = 29 Ib = 30	Breast cancer survivors self-reporting cognitive symptoms. All were ≥ 40 years old, post-menopausal, and ≥ 1 year post adjuvant chemotherapy.	C: Wait list Ia: Memory training teaching strategies for remembering word lists, sequences, and texts by applying meaningfulness, organization, visualization, and association. Ib: Speed of processing training using Insight program.	Ia showed better immediate (ES 0.59 p = .036) and delayed (ES 0.7, p = .013) memory performance at 2 months. Ib showed better processing speed post-intervention (ES 0.55, p = .04) and 2 months (ES 0.67, p = .016); and immediate memory at both time points (p = .007; p = .004). Both interventions improved aspects of cognitive symptoms compared to C.	Small sample size

Table 3 (continued)

Author, year, country	Study design, Number (*n*)	Population	Intervention summary	Outcomes	Notes
Cognitive rehabilitation					
Ercoli 2015 [121] USA	Randomized phase II study *n* = 48 *C* = 16 *I* = 32	Women with breast cancer stage 0-III completed primary treatment 18–60 months prior, aged 25–75 years; cognitive symptoms	C: Wait list I: Cognitive rehabilitation – 5 x 2 h/week manualized program addressing targeted attention, executive function, memory, and a review. Total dose 10 h	Verbal learning scores improved in I (p = .02–.07) over time. Cognitive symptoms improved in I (p = .01).	Randomized phase II study, suggests efficacy
King 2015 [122] Australia	RCT *n* = 29 *C* = 13 *I* = 16 Community control: 16	Adult cancer survivors (non-CNS) completed treatment ≥ 6 months.	C: Waitlist control I: RECOG, 4-week cognitive rehabilitation program delivered online involving skills training, compensatory strategies, group discussion, and homework Total dose 8 h	I group improved speed of information processing compared to C (p = .005). Cognitive symptoms improved overtime across both cancer groups, I group significantly greater improvement at end of intervention.	Non-randomized community control Small sample size with multiple comparisons
Mihuta 2018 [124] Australia	RCT *N* = 59, 51 did T1 (44 analyzed) *I* cancer = 16, 12 (12) I non-cancer = 23, 21 (16) *C* non-cancer = 20, 17 (15)	Cancer: adult cancer (non-CNS), primary treatment finished ≥ 6 months, cognitive symptoms. Non-cancer: aged ≥35 years	C: Waitlist (non-cancer only) Ic: RECOG, 4-week cognitive rehabilitation program delivered online involving skills training, compensatory strategies, group discussion, and homework Inc: RECOG (see above) Total dose 8 h	PCI improved over time in Ic and Inc groups (p < .001); effect maintained at 3 months (p = .033). Ic improved attention but Inc declined.	Non-randomized cancer group Small sample size with multiple comparisons
Ferguson 2016 [144] USA	RCT (number analyzed) *n* = 47 (35) *C* = 20 (13) *I* = 27 (22)	Breast cancer, Stage I, II or IIIA, completed adjuvant chemotherapy ≥ 6 months prior	C: Supportive therapy I: MAAT Both delivered via videoconference.	MAAT group showed: improved PCI at 2-months (ES 0.52, p = .02) improved processing speed (ES 0.50, p = .03) but not verbal memory (p = .84)	Small study with large attrition Duration of effect not assessed beyond two years Mixed results on neuropsychological assessment
Park 2017 [145] Korea	Pilot quasi--randomized trial *n* = 62 (analyzed 54) *C* = 31 (27) *I* = 31 (27)	Breast cancer, Stage I-II, scheduled for high-dose adjuvant chemotherapy, aged 20–60 years at diagnosis	C: Wait List I: Compensatory strategies training – PCHP	PCHP demonstrated improved objective cognitive function, memory, and executive function compared to control over time; PCI remained stable over time for PCHP compared to C	Treatment allocation via raffle (odds and even numbers) Small sample size and high attrition rate
Mind-body (mindfulness meditation, neurofeedback, acupuncture)					
Johns 2016 [133] USA	Pilot RCT *n* = 71 *C* = 36 *I* = 35	Breast or colorectal cancer survivors, stage 0–III treated with chemotherapy +/- radiation therapy, Clinically significant CRF	C: Fatigue education and support 8× weekly sessions, 2 h/week I: MBSR 8 x weekly sessions, 2 h/week	I improved AFI (self-report subjective endpoint) post-intervention (p ≤ .004), sustained at 6-months (p < .027). No difference in neuropsychological performance.	Sample predominantly breast cancer Small sample size Unblinded assessments Inclusion criteria based on fatigue rather than cognition
Johnston 2011 [135] USA	Pilot RCT *n* = 13 *C* = 7	Breast cancer survivors completed primary	C: Usual care I: Self-care training (4× weekly sessions),	No change in cognitive symptoms between groups.	Primary endpoint fatigue Non-blinded study

Table 3 (continued)

Author, year, country	Study design, Number (*n*)	Population	Intervention summary	Outcomes	Notes
	I = 6	therapy, ≥ 4 on BFI, aged 18-65 years.	holistic assessment and tailoring of IM advice plus acupuncture 8x weekly sessions.		Small sample size
Alvarez 2013 [134] USA	Quasi-experimental trial using waitlist control *n* = 23	Breast cancer survivors with self-reported cognitive impairment since diagnosis and treatment with chemotherapy (time since chemotherapy ranged 9–59 months)	I: Single EEG electrodes at left C3 and right C4 analyzes changes in brain phase states while subject listens to music; no subject response required as brain uses the feedback for its own self-organization without consciousness. Requires 20 sessions over 10 weeks.	Initial significant improvement in perceived cognitive impairment, comments from others, perceived cognitive abilities, and impact on quality of life (FACT-Cog $p < .001$); perceived cognitive abilities remained significantly improved 4 weeks after intervention conclusion	Small sample size Unblinded No random assignment Specialized equipment and training required for intervention use No objective cognitive performance measurement
Cimprich/Ronis 2003 [137] USA	RCT *n* = 157 *C* = 74 *I* = 83	Newly diagnosed early stage breast cancer	C: Usual care I: 120 min/week of natural environment, home-based program	Significant improvement in attentional capacity ($p < .05$) from 17 days prior to surgery to 19 days post-operative	Breast cancer subjects only Surgical procedures only Unblinded
Cimprich 1993 [136] USA	RCT pilot *n* = 32 *C* = 16 *I* = 16	Stage I or II breast cancer survivors 3 months post-operative	C: Usual care I: 120 min/week of natural environment, home-based program	Significant improvement in attentional capacity ($p < .05$) across all 4 time points up to 90 days	Breast cancer subjects only Surgical procedures only Small sample size Unblinded
Freeman 2014 [130] USA	RCT (waitlist controlled) *n* = 118 *C* = 47 *I* = 71 (Live delivery = 48; teleconference = 23)	Breast cancer survivors (all stages) 6-week post-treatment completion	I: 5 weekly 4-h group sessions delivered live or teleconference providing guided imagery training (didactic and practice); weekly calls during and throughout 3 months post-intervention completion to encourage daily imagery practice	Live & telemedicine groups reported better cognitive function ($p < .01$); there were no differences between live and teleconference group for cognitive function or other QOL outcomes	Unblinded No appropriate attentional control Training required for intervention delivery No objective cognitive performance measures
Hoffman 2012 [132] UK	RCT (waitlist controlled) *n* = 214 *C* = 111 *I* = 103	Stage 0 to III Breast cancer	C: Usual care I: 2–2.25-h sessions over 8 weeks consisting of mindfulness techniques (didactic & practice) and 1 session involving a 6-h day of mindfulness; home practice using four 45-min CDs for use 6–7 times per week	Significantly reduced confusion (POMS $p = .002$)	Unblinded No appropriate attentional control No objective cognitive performance measures
Milbury 2013 [131] USA	RCT (waitlist controlled) *n* = 47	Stage I to III breast cancer survivors with self-reported cognitive impairment, 6 to 60 months post-chemotherapy completion	I: 12 1-h Tibetan sound meditation sessions over 6 weeks incorporating didactic and practice (deep breathing, awareness, concentration, visualization); home practice encouraged using CD and printed materials	No significant differences in objective or subjective cognitive function between intervention or control groups were found although the intervention group performed better on verbal memory ($p = .06$), short-term memory ($p =$	Small sample size No appropriate attentional control group

Table 3 (continued)

Author, year, country	Study design, Number (*n*)	Population	Intervention summary	Outcomes	Notes
				.09), and processing speed (p = .09), and reported improved cognitive function (p = .06) and abilities (p = .08) at end of intervention which was not sustained one month later	

AFI, Attentional Function Index; *BFI*, Brief Fatigue Inventory; *BRIEF*, Global Executive Composite score of the Behavioral Rating Inventory of Executive Function; *C*, Control; *CBT-I*, Cognitive behaviour therapy for insomnia; *CD*, Compact disc; *CNS*, Central Nervous System; *CRF*, Cancer related fatigue; *EEG*, electroencephalography; *EF*, executive function; *EORTC-CFS*, European Organisation for research and Treatment of Cancer-Cognitive Functioning Scale; *ES*, Effect size; *FACT-Cog*, Functional Assessment of Cancer Therapy-Cognitive; *I*, Intervention; *IM*, Integrative medicine; *MAAT*, Memory and Attention Adaptation Training; *MBSR*, Mindfulness-based stress reduction; *PA*, Physical activity; *PCHP*, Promoting Cognitive Health Program; *PCI*, Perceived Cognitive Impairment; *QOL*, Quality of life; *RCT*, Randomized controlled trial; *RECOG*, Responding to cognitive concerns; *UC*, Usual Care

reported by breast cancer survivors using in-person training delivered in a group setting [118]. Similarly, another study demonstrated improvement in speed of processing immediately- and 6 months-post intervention in breast cancer survivors compared to waitlist controls using a home-based training intervention [114]. In the largest study to date, a home-based cognitive training intervention improved self-reported cognitive concerns but not objectively measured cognitive performance in 242 solid tumor cancer survivors, though 14% of participants enrolled in this pragmatic trial did not complete the program [117]. Given that cognitive training interventions assume consistent participation in the training activities, barriers to adherence may include time demands, depression, or other health problems [119].

Cognitive rehabilitation programs involve the development of individualized skills to support cognitive deficits, assist with problem-solving, and improve or restore functioning. Components of these programs include the use of cognitive aids and the development of cognitive skills, along with metacognitive strategies designed to increase individual self-awareness. For example, to support memory deficits, aids such as diaries and alarms may be used to help with organization and appointments, while cognitive skills such as chunking may be useful for remembering telephone numbers. The effect of cognitive rehabilitation interventions has been tested in several studies of non-CNS cancer survivors [120–125]. These interventions were delivered on either an individual or group format over multiple sessions, including one or more elements of cognitive training, compensatory strategies, and mindfulness. All demonstrated improved perceived cognitive functioning, but mixed results for neuropsychological performance, similar to non-cancer control participants. Recent systematic reviews provide detailed examination of the current evidence regarding the cognitive training and rehabilitation for CRCI [126, 127].

Exercise Exercise is associated with decreases in a range of cancer-related physiological and psychological symptoms and has been shown to be beneficial for neurological function. Multiple clinical trials have investigated the role of exercise on CRCI, as summarized in recent systematic reviews [128, 129]. Overall, there is some evidence of exercise-related improvements in self-reported cognitive functioning and neuropsychological performance, that does not appear to be limited to a particular type of exercise (e.g., aerobic, resistance, mixed, yoga) [129]. However, most studies have evaluated effects on CRCI as a secondary outcome, and substantial heterogeneity across studies, particularly for exercise modalities, makes comparison of studies difficult.

Mind-body Mind-body interventions are designed to bring an awareness of one's individual potential for healing or restoration. The mind-body intervention categories aimed to improve cognitive function in cancer survivors include guided imagery [130], meditation [131], mindfulness-based stress reduction (MBSR) [132, 133], neuro/biofeedback [134], acupuncture [135], and restorative environment [136, 137]. Meditation, MBSR, and restorative environment interventions yielded improved objective cognitive performance for domains of short-term and verbal memory [131], speed of processing [131],

Table 4 Clinical trials of pharmacological interventions for CRCI in non-CNS cancers

Author, Year, Country	Study design, Number (*n*)	Population	Intervention summary	Outcomes	Notes
Methylphenidate					
Mar Fan 2008 [146] Canada	RCT *n* = 57 *C* = 28 *I* = 29	Breast cancer Plan for at least 4 cycles of adjuvant chemotherapy	C: Placebo I: d-methylphenidate 5 mg bid; after 1 week increased to 10 mg bid if tolerated Participants randomized after first cycle and continued until end of final cycle of chemotherapy	No differences in global cognitive function (MMSE, High Sensitivity Cognitive Screen) or memory (HVLT-R)	Study closed prematurely due to slow accrual High Sensitivity Cognitive Screen has substantial practice effect
Lower 2009 [147] USA	RCT *n* = 154 *C* = 78 *I* = 76	Cancer survivors who completed at least 4 cycles of chemotherapy at least 2 months prior to study	C: Placebo I: d-methylphenidate 5 mg bid Administered over 8 weeks	No differences in cognitive function between groups or over time. Higher rate of drug-related adverse events (63 vs. 28%) and discontinuation rate due to adverse events (11% vs. 1.3%, $p = .02$) in d-MPH group	Study powered to detect changes in fatigue (primary outcome) not cognitive function
Escalante 2014 [148] USA	RCT *n* = 57	Female patients with breast cancer 84% currently receiving chemotherapy	C: Placebo I: methylphenidate-SR 18 mg/d In one arm, participants received MPH × 2 weeks, then placebo × 2 weeks In other arm, received placebo × 2 weeks, then MPH × 3 weeks	Compared to placebo MPH was associated with better cognitive processing (WAIS-III digit span, $p = .01$) and less confusion (POMS, $p = .05$).	Small sample size
Modafinil					
Kohli 2009 [139] USA	Prospective, open-label clinical trial *n* = 68 *C* = 34 *I* = 34	Female breast cancer patients being treated with surgery and chemotherapy	C: Placebo I: Modafinil 200 mg/d In phase I, all participants were given modafinil 200 mg/d × 4 weeks. Those with positive response were randomized to either modafinil 200 mg/d or placebo × 4 weeks	In phase I, modafinil had a significant effect on speed of memory (p = .0073) and quality of episodic memory ($p = .0001$) In phase II, those who continued on modafinil demonstrated greater improvement in cumulative speed of memory ($p = .029$), quality of episodic memory ($p = .0151$), and continuity of attention ($p = .0101$) compared to placebo	Findings were from secondary analysis Open-label Small sample size Cognitive Drug Research measure has not been validated in cancer
Lundorff 2009 [149] Denmark	RCT *n* = 28	Patients with advanced cancers (both hematologic and solid tumors) enrolled in palliative care	C: Placebo I: Modafinil 200 mg/d Randomized to placebo or modafinil x 3 days, then crossover to other arm × 3 days	Compared to placebo, patients in modafinil group with improvements in psychomotor speed with dominant hand (FTT, $p = .006$) and executive function (TMT-B, $p = .042$)	Short duration between med administration and assessment No conclusions can be made about long-term use
Donepezil					
Lawrence 2016 [140] USA	RCT *n* = 62 *C* = 31 *I* = 31	Women with breast cancer who received adjuvant chemotherapy (> 4 cycles) 1–5 years prior Self-reported cognitive dysfunction	C: Placebo I: Donepezil 5 mg/days × 6 weeks, then 10 mg/d x 18 weeks	Donepezil group performed better than control in multiple measures of memory (HVLT-R Total Recall, $p = .033$; HVLT-R Discrimination, $p = .036$)	Small sample size Not powered to detect efficacy
Selective serotonin reuptake inhibitors					
Li 2014 [143] China	Non-randomized controlled trial *n* = 122 *C* = 36	Patients with advanced cancer (GI, hematologic, lung)	C: Supportive care I: Sertaline 25–75 mg qd × 12 weeks	At baseline depressed patients with worse executive function (WCST, $p < .01$), but after administration of sertraline, no	High levels of depressive symptoms were required to be

Table 4 (continued)

Author, Year, Country	Study design, Number (*n*)	Population	Intervention summary	Outcomes	Notes
	I = 86			significant difference between groups	assigned to the intervention group Doses varied
Vitamin E					
Chan 2004 [142] China	Non-randomized, open-label controlled trial *n* = 29 *C* = 10 *I* = 19	Patients with nasopharyngeal carcinoma and temporal lobe radionecrosis	C: Usual care I: Vitamin E 1,000 IU bid × 1 year	In Vitamin E arm, significant improvement from baseline in global cognition (MMSE, p = .035), verbal memory (HKLLT, p = .036), visual memory (WMS-VR, p = .007), executive function (computerized reaction time, p = .001; cognitive flexibility test, p = .04) No improvements in control group	Small sample size No randomization, blinding, or placebo Gender difference between C and I arms
Ginkgo Biloba					
Barton 2014 [150] USA	RCT *n* = 210 *C* = 107 *I* = 103	Breast cancer patients receiving adjuvant chemotherapy	C: Placebo I: Ginkgo biloba 60 mg bid. Administered from prior to the second cycle of chemotherapy through 1 month after chemotherapy completion	Ginkgo biloba did not prevent cognitive decline	Participants had already begun chemotherapy Global cognitive measure (HSCS) has a large practice effect
Erythropoietin-stimulating agents					
Chang 2004 [151] Canada	RCT *n* = 354 *C* = 178 *I* = 176	Patients with metastatic breast cancer receiving adjuvant chemotherapy	C: Standard of care I: epoetin alfa 40,000 IU weekly × 16 weeks or until 4 weeks after completion of chemotherapy (whichever was longer, maximum 28 weeks)	Significant improvement in cognition (HUI3 utility scale, p = .02) between baseline and to week 12 in EPO group compared to SOC	No objective measures HUI3 not widely used for measurement of self-reported cognitive function

AFI, Attentional Function Index; *BFI*, Brief Fatigue Inventory; *BRIEF*, Global Executive Composite score of the Behavioral Rating Inventory of Executive Function; *C*, Control; *CBT-I*, Cognitive behaviour therapy for insomnia; *CD*, Compact disc; *CNS*, Central Nervous System; *CRF*, Cancer related fatigue; *EEG*, electroencephalography; *EF*, executive function; *EORTC-CFS*, European Organisation for Research and Treatment of Cancer-Cognitive Functioning Scale; *ES*, Effect size; *FACT-Cog*, Functional Assessment of Cancer Therapy-Cognitive; *I*, Intervention; *IM*, Integrative medicine; *MAAT*, Memory and Attention Adaptation Training; *MBSR*, Mindfulness-based stress reduction; *PA*, Physical activity; *PCHP*, Promoting Cognitive Health Program; *PCI*, Perceived Cognitive Impairment; *QOL*, Quality of life; *RCT*, Randomized controlled trial; *RECOG*, Responding to cognitive concerns; *UC*, Usual Care

executive function [121], and attentional control [121, 136, 137]. Improvements in subjective cognitive function have also been observed [130–132, 134, 136, 137].

Pharmacotherapies The utility of pharmacological agents to treat CRCI in the context of non-CNS cancers has yet to be established and remains an area of limited research [138]. Pharmacotherapies evaluated for this purpose, mainly in the context of breast cancer or advanced non-CNS cancer, include stimulants (e.g., methylphenidate and modafinil), medications used for Alzheimer's disease (e.g., donepezil and memantine), selective-serotonin reuptake inhibitors (e.g., sertraline and paroxetine), ginkgo biloba, and vitamin E. Though pharmacotherapies have not demonstrated consistent benefits for CRCI, improvements to specific cognitive domains have been reported. For example, objectively measured benefits in memory associated with modafinil [139], donepezil [140], memantine [141], and vitamin E [142]. Deficits in executive function have responded to trials of memantine [141], sertraline [143], and vitamin E [142]. Further research is needed in larger and more heterogeneous patient samples, using more sophisticated measurement techniques.

Evaluating the effectiveness of various CRCI interventions is restricted by the early stage of the current evidence base: small samples, lack of non-breast cancer participants, variability in comparison groups, and limited long-term follow-up. Evidence of efficacy is further limited by study heterogeneity for intervention characteristics (e.g., dose, delivery format, timing), measurement of CRCI outcomes, and methodological rigor, making comparison across studies difficult, including using meta-analytic methods that could help establish the relative effectiveness of these interventions. Rigorous, adequately powered, randomized, and appropriately controlled trials are needed to build on the existing research to support evidence-based decision making to the allocation of these interventions in clinical practice.

Conclusions

CRCI has a multifactorial origin comprising neoplastic processes, traditional cytotoxic chemotherapy and radiation therapy, novel therapies, and the synergistic consequences of these factors. Consequently, no one simple intervention exists to prevent, preserve, and improve CRCI. Potential therapies and strategies should be targeted towards multiple specific pathophysiological mechanisms. Early identification of clinical signs of cognitive decline through self-report questionnaires and cognitive testing may aid the oncology providers, patients, and their caregivers in shared decision-making regarding supportive strategies to minimize the functional impact of CRCI.

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Data Availability Not Applicable

Compliance with ethical standards

Conflict of interest Dr. Loprinzi reports personal fees from PledPharma, personal fees from Disarm Therapeutics, personal fees from Asahi Kasei, personal fees from Metys Pharmaceuticals, personal fees from OnQuality, personal fees from Mitsubishi Tanabe, personal fees from NKMax, personal fees from Novartis, outside the submitted work. All other authors declare that they have no conflict of interest.

Code availability Not Applicable

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