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Embracing the complexity: Older adults with cancer-related cognitive decline- - A Young International Society of Geriatric Oncology Position Paper.

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Abstract

Cancer-related cognitive decline (CRCD) may have particularly significant consequences for older adults, impacting their functional and physical abilities, level of independence, ability to make decisions, treatment adherence, overall quality of life, and ultimately survival. In honor of Dr. Hurria’s work we explore and examine multiple types of screening, assessment and non-pharmacologic treatments for CRCD. We then suggest future research and clinical practice questions to holistically appreciate the complexity of older adults with cancer’s experiences and fully integrate the team-based approach to best serve this population.

Keywords

Cancer-related Cognitive Decline; Rehabilitation; Older Adults; Assessment

Introduction

Due to advances in screening, early diagnosis, and improved anticancer treatments, there is an increasing prevalence of cancer survivors, and in turn, an increased concern about the late effects of cancer treatments. A common effect of cancer treatment is cancer-related cognitive decline (CRCD), sometimes referred to as “chemobrain” or “chemofog”, which can persist long after treatment completion. Cognitive problems may have particularly significant consequences for older adults with cancer, impacting their functional status, level of independence, decision-making capacity, treatment compliance, quality of life, caregiver burden, and ultimately survival [1–3]. Inspired by Dr. Hurria’s pioneering work in the field of CRCD research and her legacy of improving the care of older adults with cancer by embracing the complexity of their experiences, we aim to examine the evidence on the assessment and interventions of CRCD, and to document critical research gaps and areas of improvement. In honor of her integrative and collaborative approach to patient centered care, we have included multiple disciplinary perspectives and approaches as we provide recommendations to implement her visionary work in CRCD in older adults.

Research in the transactional influences of cancer, treatments and cognitive aging on the brain are complex and their role in CRCD in older adults is growing. CRCD is observed across a range of cognitive domains, such as executive functioning, memory, processing speed, and attention, which are also subject to the effects of aging on the brain itself [4, 5]. In looking beyond the interaction of cancer and normal aging, Drs. Hurria and Ahles, as well as others, have proposed that anticancer treatments can influence and accelerate the trajectory of cognitive aging [6–10]. Prevalence estimates of CRCD in adult cancer survivorship vary depending on the assessments used, definition of impairment, or decline, employed, and cancer type, but are generally fairly high: brain tumors: up to 90%; leukemia: 20–30%; breast cancer: 40%; gynecologic cancer: 60%; head and neck cancer: 38%; colorectal cancer: 40%; testicular cancer: 60% [11–19]. Cognitive impairment is also reported in adults with thyroid cancers [20], however, for men with prostate cancer, with an average age of diagnosis at 66, the association between cognitive impairment and androgen therapy remains debated [21].

As highlighted by Hurria et al. [22, 23], patient-related factors (psychological status, fatigue, mental health, functional age, menopause, comorbidities and preexisting cognitive impairments) may be useful in predicting those at greatest risk for CRCD. The presence of pre-treatment depressive symptoms, anxiety, higher levels of fatigue, lower functional well-being, reduced cognitive reserve and post treatment endocrine therapy have also been found to be predictors of cognitive decline in adults with breast cancer who have received chemotherapy, but are not conclusive or consistent [24–31]. Furthermore, older women with breast cancer who have cognitive decline are more likely to discontinue adjuvant endocrine treatment [32], and cognitive decline is significantly associated with frailty during treatment [33]. In addition, post-operative delirium in older adults is associated with a poorer trajectory of cognitive function after surgery, as well as increased risk for later dementia [34, 35]. Since many older patients with cancer are likely to undergo surgery, particular attention to preventing post-operative delirium is important [36]. Lastly, the high prevalence of polypharmacy and the frequent use of potentially inappropriate medications in older adults with cancer is a concern for contributing to worsening cognition, but there are limited data on this to date [37, 38].

Although there are many gaps in our knowledge on CRCD, several recent studies have improved our understanding of the pathophysiology as well as associated risk factors. Evidence from cross-sectional and longitudinal imaging have shown that some patients with breast cancer on chemotherapy exhibit long-term changes in frontal regions and decreases in gray and white matter volumes compared with controls (including healthy individuals and breast cancer patients not receiving chemotherapy); and, these changes correlate with neurocognitive deficits [39, 40]. Other imaging studies support the negative impact on the brain of cytotoxics used to treat breast cancer [41–45]. Preliminary research on genetic predictors indicates that apolipoprotein E4 (APOE4) allele, catechol-O-methyltransferase (COMT)-valine genotype and gene polymorphisms may also increase the risk of CRCD [46–48].

The intensity of treatments as well as the cumulative amount may affect the risk of CRCD. For example, in adults who receive hematopoietic cell transplantation (HCT), which involves conditioning treatment prior to transplantion, their rate of pre-HCT cognitive impairment can be high, and their risk of CRCD only increases after HCT, suggesting that the effect of cancer treatment on cognition may be cumulative [49–51]. The intensity of the conditioning treatment regimen may also affect the risk and timing of cognitive decline, with patients treated with more aggressive approaches (i.e. myeloablative conditioning or the use of total body radiation) being at higher risk for developing CRCD and more likely to experience persistent CRCD [52]. However, evidence on the biologic drivers of CRCD in older individuals in particular remains limited, with inadequate understanding of important and unique aging factors, such as comorbidities, polypharmacy, and cognitive reserve [19, 52–54]. Furthermore, the impact of newer cancer therapies, such as immunotherapy and other targeted agents, among older adults with cancer is extremely limited and warrants further study.

Adults with CRCD do not routinely receive attention for cognitive concerns, especially from health care providers [55]. Individuals with CRCD are then forced to adapt despite the considerable impact of symptoms across all life demands [55]. Inspired by Dr. Hurria’s work, her innovative ability for multi-disciplinary team building, and problem-solving, we will review the state of the science of CRCD assessment and non-pharmacologic treatment (given the complexity of cancer treatments and potential comorbidity load in older adults with cancer, pharmaceutical approaches are beyond the scope of this paper) in older adults and highlight future research directions for the field.

Assessment

The National Comprehensive Cancer Center (NCCN) older adult oncology guidelines, American Society of Clinical Oncology and International Society of Geriatric Oncology recommend regular assessment of cognition [56–60]. Led by Dr. Hurria, cognitive screening is a recommended part of an oncology-based routine geriatric assessments (GA) [58]. Therefore, GA also presents an opportunity for screening for CRCD in clinical trials for older adults with cancer [61]. The GA provides an opportunity to identify cognitive decline often overlooked by routine care, can better assess treatment tolerability and prognosis, and more effectively facilitate shared decision-making and improve patient engagement in order to develop personalized treatment plans [62–68]. Furthermore, GA allows for potential routine and systematic assessment of baseline cognition as part of risk stratification for patients undergoing anticancer treatment.

CRCD co-occurring within the context of age-related cognitive decline presents two immediate challenges to precise and accurate screening. First, many commonly used geriatric cognitive screeners, such as the Mini-Cog [69], Montreal Cognitive Assessment (MoCA)[70], Mini-Mental Status Exam (MMSE)[71], and Blessed Orientation Memory and Concentration (BOMC) [72], were developed to screen for dementia or to assess a focal impairment such as following a stroke. These syndromes are qualitatively different than CRCD, so the commonly used GA cognitive screeners may not be generalizable to CRCD. Among these tools, only the MoCA has demonstrated acceptable levels of sensitivity within patients with cancer [73–75]. Second, given the lack of research about their use in the context of CRCD, cut-off scores specific to adults with cancer have not been established. NCCN guidelines for assessment of cognitive impairment in older adults recommends the use of Mini-Cog and functional assessment of instrumental and basic activities of daily living [57].

A more robust and patient-centered approach to cognitive screening involves pairing screening with patient-reported outcome measures (PRO) of perception of cognitive decline [76]. Common CRCD PROs include the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog), PROMIS® Cognitive Function, and Cognitive Symptom Checklist-Work 21 (CSC-W21); however, limited data are available for their use in older adults populations with cancer [77]. When screening tests are positive for potential symptoms of CRCD, and there are cognitive concerns noted by patients, caregivers, or medical staff, more extensive assessments should be considered (e.g., neuropsychological or functional assessment). Also, when screening for CRCD in the older adult population, changes in anxiety and depression may be significant contributors [56]. Brief, self-report validated measures such as the Geriatric Depression Screen or the Mental Health Index can shed important information on cognitive complaints, as well as offer possible targets of intervention [78, 79].

Neuropsychological assessment.

If more in-depth cognitive evaluation is required, neuropsychological assessments should be considered. Neuropsychological assessment provides an quantitative as well as qualitative evaluation of factors contributing to cognitive dysfunction, including developmental history, comorbidities, psychiatric syndromes, and polypharmacy [80]. For instance, if there is suspicion of cognitive decline, neuropsychologists are trained to recognize neuropsychological patterns typical of normal aging, Alzheimer’s disease and other dementias, psychiatric disorders, and other conditions - which can inform differential diagnosis of CRCD. Neuropsychologists are also trained in evaluating problems relevant to older adults, such as vision and hearing decline, which can dramatically interfere with the testing validity [81]. The International Cognition and Cancer Task Force recommends a core set of neuropsychological tests [82] to assess CRCD.

Neuropsychological assessment can also provide reliable, valid and objective means to monitor cognitive function and changes over time which are a particularly important aspect of health monitoring in patients with central nervous system (CNS) tumors or who are undergoing treatments with cognitive risk (e.g., chemotherapy, radiation, HCT) [5]. Changes or declines in cognitive status can also signal changes in disease and health, or alert providers and family to the possibility of functional decline and raise concerns about medication adherence. Furthermore, neuropsychologists are trained to discuss cognitive limitations and disorders with patients and their families, in addition to providing targeted recommendations to optimize functioning and lessen caregiver burden. Importantly, in older adults with cancer this approach is also key to unlocking and discussing cognitive symptoms that may otherwise be minimized due to fear or embarrassment [55, 83].

Functional Assessment.

Overall changes in comorbid conditions, frailty and functioning may contribute to cognitive decline and should therefore be assessed in parallel [84, 85]. While the GA provides valuable understanding of an older adult's basic functional age, it is equally important to evaluate how physical, psychological and cognitive factors can impact and relate to participation in life roles.

Older adults may have various degrees of co-occurring functional impairments, including restrictions in mobility or balance, low muscle mass, recurrent falls and geriatric syndromes, polypharmacy and limited social support [86]. Even minor changes in cognitive ability may potentially impact cancer survivors' ability to live independently [87]. Occupational therapists may use "functional cognition" as an assessment tool, which involves identifying how an individual utilizes and integrates thinking and processing skills to accomplish everyday activities in clinical and community living environments [88]. Occupational therapy practitioners can evaluate how an older adult with cancer integrates cognitive skills into daily activities such as self-care, instrumental activities of daily living (e.g. medication management, driving, household tasks), work, leisure, and social participation through function-based cognitive assessments and evaluation of performance and perception of daily living skills. Evaluating how cognitive changes interfere with daily functioning is necessary to determine compensatory or remedial interventions, especially as the impact of cognitive changes on daily activities changes over time.

Prevention and Rehabilitation Interventions

Physical Interventions.

Non-pharmacological approaches have an increasing amount of evidence highlighting the health benefits of exercise, both in healthy adults and cancer survivors [89–94]. The recent release of the Second Edition of the Physical Activity Guidelines for Americans highlighted improved cognition with exercise across the lifespan, with more robust associations in older adults [95]. Several recent reviews have highlighted the utility of physical activity to mitigate aging-related declines in cognitive function [96–98]. These studies span cross-sectional work, randomized controlled trials, and epidemiologic studies of large cohorts.

Regular physical activity in community-dwelling older adults has been associated with increased brain volume and cortical plasticity, and improved cognitive vitality and associated neural circuitry and functioning [99–102]. Results from cross-sectional human and animal studies have demonstrated an association between increased physical activity and less CRCD associated with treatments for cancer [103]. Therefore, physical activity (i.e., daily cumulative activities requiring physical function) and/or exercise (i.e., physical activity intentionally performed to improve an aspect of fitness and/or health) have been proposed as a potential non-pharmacologic primary prevention for CRCD.

The positive associations between regular physical activity and cognitive function may be due to lower levels of inflammation, increased neurotransmitters and neurotrophins, and increasing structural adaptions in the CNS [104, 105]. Additionally, exercise is associated with an improvement of other chronic conditions that potentially affect cognition, such as depression, sleep disruption and obesity [106]. Results from animal studies have indicated that exercise can attenuate CRCD and neuroplasticity in cancer, particularly during chemotherapy treatment [107]. However, results have been difficult to translate to a human model, and interventional studies have been limited by design, owing to incomplete randomization and lack of control groups, missing data and variable use of assessment tools [103].

More recently, researchers have attempted to explore the effects of exercise on cognition specifically in cancer survivors. To date, less than 30 studies in humans have examined the association between exercise and cognitive function specific to cancer, and very few were intervention trials [103, 104]. The majority of studies have associated aerobic, resistance, and combination exercise interventions with positive [108–113] effects on both objectively and subjectively measured cognition for adults with cancer. [104]. Specifically, resistance exercise has been associated with improvements in objectively measured domains of concentration and cognitive flexibility [112]. Combined interventions, including aerobic exercise and sustained attention tasks, have been associated with improved cognitive flexibility and inhibitory control for older adults with cancer, which are important determinants of executive functions [108]. Notably, no detrimental effects of exercise on CRCD have been documented [90, 91, 114]. However, these studies are limited by significant variation in the instruments used to measure cognitive function, focus on younger adults who do not typically have cognitive impairment prior to therapy, and variance in the domains f cognitive function that were measured across studies [104].

The relationship between physical activity and cognitive function is complex, particularly in older patients with cancer, due to the accelerated aging effects of cancer and its treatment. [103]. A major limitation of physical activity interventions after cancer is that these studies are not specific to older cancer survivors. Therefore the results may not be generalizable to older adults who may experience additive effects of age-related and CRCD [108]. More research is needed on the type, intensity, frequency, and duration of exercise to improve cognitive outcomes [115], including traditional exercise models and mind-body components (e.g., yoga, tai chi). Several studies published in the past few years suggested that further replication and extension of these findings is forthcoming [116–119]. Despite these mixed findings and calls for more rigorous methodology, the National Comprehensive Cancer Network has recommended exercise as a management strategy for CRCD [120].

Integrative approaches.

Some mind-body practices and lifestyle modifications represent a promising behavioral approach to counteract CRCD, although their efficacy has yet to be specifically tested for older adults with cancer. Integrative approaches differ from aerobic exercise since they more directly target directed breathing, postures, and meditation [103]. Altogether, integrative approaches used in oncology, (such as Qigong, and Tai-chi) have been established to mitigate CRCD and improve quality of life [121, 122], and therefore could be considered as a potential resource to improve cognition. However, the underlying mechanisms of such interventions remain unclear; cognitive benefits may be due to stress-reduction pathways in the brain or mitigation of posttraumatic stress, emotional status, fatigue, and sleep disorders.

Tai chi is ideal for older adults with cancer who are either unable or reluctant to exercise because of weakness or fatigue [103]. Tai chi involves slow movement sequences coordinated with breathing and focused attention and can reduce falls and improve gait and balance [123]. A recent meta-analysis of Tai Chi interventions in cancer care identified three previous studies examining cognitive function and showed an overall positive effect [124]. The average age of paticipants ranged from 59–66 years old, demostating some evidence that Tai Chi may be beneficial for CRCD in older adults with cancer. Yoga interventions have also demonstrated generally positive effects on CRCD [103]. In fact, two of the largest human interventional trials aimed at improving CRCD have leveraged yoga as the intervention of choice [125, 126]. Despite these preliminary positive results, the yoga-CRCD association is unclear in older cancer populations specifically, warranting more research in this space.

Mindfulness-based.

Mindfulness-based interventions are integrative therapeutic practices based on meditation with a focus on present-moment experience in the context of openness, curiosity, and acceptance. Mindfulness is effective in improving CRCD in cancer patients [127], but also working memory and attention in non-cancer populations [128]. It additionally affects sleep, quality of life, depression, anxiety and fatigue [129], however the majority of participants have been younger than 65 years-old [130]. A recent systematic review examining mindfulness interventions for CRCD in breast cancer survivors found some evidence of effectiveness, and recommendations included using validated comprehensive measures of cognition, as well as further research into the timing, duration and content of mindfulness interventions [131]. These studies suggest that mindfulness is likely an effective intervention targeting CRCD; however, further studies are needed focusing on both older adults and comparing mindfulness-based interventions to other behavioral interventions.[130].

Functional.

A function-oriented approach to rehabilitation of older adults with CRCD can maximize independence across a wide range of daily activities, including self-care and instrumental activities of daily living, work, leisure and social participation. Remedial or compensatory interventions may also be provided by an occupational therapist to address the specific physical, psychological, and lifestyle needs of survivors living with CRCD in the context of activities meaningful to them such as, management of medications and finances, home maintenance, driving, caregiving and social participation. Given the importance of the social environment in addressing cognitive health, minimizing social isolation and loneliness, while increasing social participation may improve cognitive function in cancer survivor, especially in older adults [132–134].

Cognitive-Behavioral.

Cognitive-behavioral therapy and training can improve symptoms of CRCD by identifying and addressing the behaviors, feelings, and beliefs associated with the resulting stress of cognitive complaints and can be completed by rehabilitation counselors and occupational therapists. Memory and Attention Adaptation Training (MAAT) uses a cognitive-behavioral approach to teach patients adaptive strategies to cope with cognitive issues. It involves self-awareness, self-regulation, relaxation training, activity scheduling, pacing, education on memory and attention, and cognitive compensatory strategies training [135–137]. MAAT has demonstrated improved outcomes in verbal memory, processing speed, spiritual and emotional well-being for adults with cancer [136, 138] but has not been specifically tested in older adults.

Cognitive rehabilitation and training.

Cognitive training interventions focus on abilities such as processing speed, reasoning, and memory [139], and have shown positive effects on cognition for community-dwelling older adults and adults with breast cancer [139–141]. Cognitive training interventions can include computer-based exercises aimed at increasing executive function skills such as cognitive flexibility, processing speed, working memory, and verbal fluency [140, 141]. Moreover, they may include practicing cognitive skills in everyday contexts and training in compensatory strategies [142]. They may incorporate components of stress management, memory remediation strategies, and self-efficacy training as part of the rehabilitative intervention [143]. A previous pilot study that adapted a memory-training intervention for older adults to cancer-specific needs found moderate but non-significant effects of memory-training on CRCD when compared to a health promotion control group [143]. Specific improvements were seen in memory strategies and complaints, and were accompanied by reductions in depression and anxiety; however, this study was conducted on a small cohort. More research is warranted to determine if cognitive training may be a recommended approach to mitigating CRCD in older cancer survivors specifically.

Future Areas of Research

In 2011, Dr. Hurria published an editorial in the Journal of Clinical Oncology entitled Embracing the Complexity of Comorbidity [144]. She called for understanding and capturing the impact of comorbidities on individual patients as well as integrating this information into clinical trials to gather the necessary information to inform treatment decisions. As we examined the gap areas in the field of CRCD and older adults, we found there were many opportunities to continue to better understand and capture the impact with improved and targeted assessment and interventions. Maintaining independence and cognitive ability are highly valued by older adults with cancer throughout their cancer trajectory [145]. Despite the threat to sustained independence, CRCD symptoms can be neglected by healthcare providers and become a major source of patient frustration [55, 146].

Previous research has focused on a better understanding for the mechanisms behind cognitive impairment and the impact of potential confounders, on the role of physical activity and exercise, and on specific physical, psychosocial and mind-body interventions. Much work still remains to be done to better appreciate the complexity of aging and CRCD.

We suggest examining methodological questions as a fruitful target for further research. The need for standardized screeners that could be incorporated into a GA, as well as the role of PROs in assessment are important to develop a sense of what type of assessment is the most sensitive screener with least patient and clinician burden. We need standardized CRCD screening tools and to develop better assessment approaches that integrate self-reported cognitive dysfunction. It is also critical to develop better means of capturing the functional changes associated with cognitive symptoms in older cancer patients, even, and perhaps especially, if they don’t reach the level of severity of dementia.

In the field of pediatric oncology, assessments and interventions target cognitive abilities related to specific meaningful life roles [147]. We suggest extrapolating this to older patients with CRCD, so that assessment approaches identify meaningful roles and activities, such as those related to leisure, social participation and life-space, as well as instrumental activities of daily living. Potential interventions for CRCD could include a multi-disciplinary, team-based approach involving rehabilitation clinicians, audiologists, speech and language pathologists, physical therapists, occupational therapists, clinical psychologists and neuropsychologists aiming to facilitate maintained independence. Further research is needed to demonstrate the efficacy of function-based interventions on CRCD and in addition, we suggest research also test multi-modal interventions for example, combining mindfulness meditation with graded exercise and physical activity (based on symptoms).

Finally, a multidisciplinary team is necessary to adequately address, clinically, the unique and complex needs of older adults with cancer. Just as Dr. Hurria’s work embracing the complexity of the older cancer patient led to the importance of translating the GA and comorbidities into geriatric oncology in the community and cancer centers, the complexity of CRCD in the older cancer patient requires future research to embracing multiple disciplines to extend our understanding. In the spirit of extending Dr. Arti Hurria’s work, we must listen to our patients’ struggles and engage with researchers in fields outside of oncology medicine, establishing collaborations beyond our traditional clinical and research partners to include neuroscience and rehabilitation [148]. Together, we can continue to strive to better serve older adults with cancer.

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