

The Future of Geriatric Oncology Research: Moving Toward Interventions and Objective Biomarkers of Aging

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Significant progress has been made in the field of geriatric oncology in recent years with the development and validation of a cancer-specific geriatric assessment (GA), establishing chemotherapy toxicity prediction tools, and geriatric screening tools that could be easily incorporated into a busy oncology practice.¹ With strong advocacy from guidelines, the oncologic community has begun to acknowledge the utility of these tools and explore their incorporation into the care of older adults with cancer. As we aspire to advance the field of geriatric oncology, it is time to think beyond assessments and focus research efforts on interventions and novel objective methods to evaluate patients.

In this issue of *JNCCN*, Rosko et al² present a pilot study focused on testing an exercise intervention aimed at improving functional status of older adults with hematologic malignancies receiving active therapy. Enrolled patients completed a GA, quality-of-life (QoL) evaluation, an objective measurement of function with Short Physical Performance Battery at baseline, and 4 and 6 months of the Otago Exercise Programme (OEP). Thirty patients with a median age of 75 years, most of whom were treated for plasma cell dyscrasia, were enrolled. Participants showed improvement in functional status, physical health scores, patient-reported Karnofsky performance status, Short Physical Performance Battery score, and QoL after the exercise intervention. These results demonstrate the ability of a proactive exercise program to mitigate functional decline and improve QoL during intense anticancer treatments.

Cancer diagnosis and treatments can have detrimental effects on the functional status of older adults, increasing the risks of falls, loss of independence, and frailty.³ Hence, proactive evaluation of functional status and appropriate interventions (eg, referral to physical and occupational therapy) have been proposed by guidelines.^{4,5} The Otago Exercise Programme was designed as a strength and balance retraining program aimed at preventing falls in community elders, and has been shown to reduce risk of falls and death among these individuals.⁶ Furthermore, this intervention has been shown to improve static, dynamic, proactive, and perceived balance among the general older population.⁷ This intervention has not been widely tested among geriatric oncology patients; nonetheless, in this study it resulted in significant benefit for older adults with hematologic malignancies. Prior studies among patients with cancer reported improvement in treatment tolerance, cancer-related fatigue, and QoL with participation in exercise programs during therapy.⁸ A few studies evaluating exercise programs specifically among older adults with cancer have shown improvement in anxiety, mood, self-reported health, and symptoms. The data presented in this manuscript add to the growing body of evidence supporting the inclusion of exercise programs in the management of older adults with cancer. It underscores the need for additional research to define the most effective exercise structure, frequency, and intensity for these patients. This opens a new era of research in the geriatric oncology field focused on active interventions tailored for older adults, their specific cancer diagnosis, and prescribed anticancer therapy.

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The exploratory analyses conducted during this study are also in line with the future directions of research in the field of geriatric oncology. The study included robust and repeated geriatric assessments. These assessments allowed for clustering of patients based on standardized values of each geriatric metric and identification of 3 categories of frailty. Furthermore, evaluation of molecular markers of aging in peripheral blood T-lymphocytes mRNA demonstrated an association between frailty and changes in T-cell immune profile. DNA extracted from peripheral blood mononuclear cells was also tested for epigenetic age, demonstrating a younger phenotypic age by epigenetic clocks compared with chronologic age in this cohort. Interestingly, patient's epigenetic age decreased or remained stable after the exercise intervention. Although these analyses were conducted on a small number of patients, which limits the ability to draw definitive conclusions, the results highlight the feasibility of obtaining objective biomarkers that can provide information on physiologic age and potentially guide treatment approach.

The aging process is complex, and chronologic age is a poor descriptor of the true physiologic age of an older patient. The GA is the gold standard tool for identification of age-related concerns that can predict survival and treatment tolerance. However, due to limited time and personnel, GA is not routinely used in most practices. Identification of an objective biomarker that can accurately determine the patient's true physiologic age could become a useful tool to help personalize therapy for older adults with cancer. Several biomarkers of aging have been studied in recent years, including inflammatory markers (eg, IL-6, C-reactive protein, tumor necrosis factor- α , D-dimer), markers of cellular senescence (eg, P16^{INK4A}), and sarcopenia. These biomarkers demonstrated correlation with frailty, functional decline, and survival.⁹ However, a clear clinical role for these markers or combination of them has not been defined. Aging clocks (ie, epigenetic clocks and proteomic clocks) have also been evaluated, mostly in epidemiologic studies showing correlation with risk of cancer development.^{9,10} Better understanding of these biomarkers and their

ability to predict for treatment tolerance, chronic toxicities, functional decline, and overall survival would allow us to use them as clinical tools to personalize cancer treatment for older adults, maximizing efficacy while reducing deleterious effects.

Similarly, devices such as electronic fitness trackers have the potential to provide objective information regarding the functional status of an older adult and assist in treatment planning.¹¹ These devices can also assist in monitoring and continuously evaluating patients during therapy, allowing for treatment adjustments, and even providing a personalized exercise prescription. The opportunity to have a thorough evaluation of patients outside their routine clinical visit can significantly increase the provider's ability to understand the patient's fitness and to provide enhanced support. Such intervention can result in significant improvement of outcomes for patients across the continuum of cancer care from active therapy to survivorship.

Rosko et al² should be congratulated on moving the needle forward in geriatric oncology research from assessment to interventions and from subjective measures to objective biomarkers of aging. The positive outcomes seen with the use of this exercise intervention should be further studied in larger cohorts and in various cancers and treatment settings. In addition, studies evaluating the predictive and prognostic ability of novel biomarkers such as aging clocks are needed to determine whether these tools can be used clinically as quick and reliable objective assessments. As we continue to improve our evidence-based management of older adults with cancer, focusing our efforts in these two areas will result in further improvement in the care of this vulnerable patient population.

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