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Guest Editorial

Advancing Survivorship in Older Adults With Cancer

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In honor of National Cancer Survivors Day, June 6, 2021, this edition of *JGMS* features several articles that advance the science of cancer survivorship in older adults and point us toward important next steps in the field. The National Cancer Institute considers survivorship to begin at diagnosis and last until the end of life (1). By this definition, adults aged 65 and older account for 64% of cancer survivors and are projected to account for 73% by 2040. With a median age of diagnosis of 66 years and decreased cancer-specific mortality from advances in detection and treatment, more and more patients with cancer are living long into their late decades. Despite this demographic shift, survivorship programs have primarily focused on the late effects of cancer diagnosed at younger ages, creating an urgent need to "geriatricize" survivorship care (2).

Recent evidence from the field of geriatric oncology has shown that incorporating the evaluation of geriatric domains into cancer care improves several aspects of survivorship in older adults. Compared to standard oncologic assessment (eg, Eastern Cooperative Oncology Group [ECOG] performance status), geriatric assessment better detects aging-related vulnerabilities, improves prediction of clinical outcomes, optimizes treatment decisions and clinician–patient communication, and reduces treatment toxicity (3–11). However, this evidence mainly pertains to the "acute" phase of survivorship, and many gaps remain in understanding the impact of cancer treatment months to years later.

Two meta-analyses in this edition provide strong evidence that assessment of medications and physical function—2 essential geriatric domains—should be routine in older cancer survivors (12,13). Chen et al. (13) report that in 39 studies, polypharmacy was statistically significantly associated with all-cause mortality, hospitalization, treatment-related toxicity, and postoperative complications. In 13 studies, potentially inappropriate medications were significantly associated with all-cause mortality. More research is needed to distinguish how much of these effects are driven by the number and type of medications versus underlying multimorbidity. However, Chen et al. highlight the importance of promoting age-friendly prescribing, and deprescribing, in oncology. Moreover, this meta-analysis calls for further study of disease–drug and drug–drug interactions in the context of the pharmacokinetic and pharmacodynamic changes that occur with advancing age (14).

Ezzatvar et al. (12) report that in 25 studies of 8109 adults aged 60 years or older with cancer, higher levels of physical function were strongly associated with a lower risk of all-cause mortality. The authors focused on studies using objective performance measures, such as gait speed and the Short Physical Performance Battery, that are well studied in general populations of older adults but understudied in older cancer survivors. Although there was heterogeneity in cancer type and treatment among these observational studies, pooled effect sizes were large when analyzing specific performance measures separately (hazard ratios [HRs] for death ranging from 0.40 to 0.61 comparing high to low physical function) and when combining all tests together (HR = 0.45, 95% confidence interval 0.35–0.57). These results highlight the predictive power of direct measures of physical function, which add substantial information to the standard clinician-reported oncologic performance status assessments like ECOG. Intact musculoskeletal and neurological systems, cardiopulmonary health, and cognitive function are all required for optimal physical performance, and the majority of cancers and their treatments affect one or many of these systems.

Most of these tests of physical function were measured prior to cancer treatment for the purpose of risk prediction, but more longitudinal studies of function as an outcome are needed. Understanding functional trajectories is especially relevant to older cancer survivors, who often value function relative to survival to a higher degree than younger survivors (15). A recent systematic review by Loh et al. (16) highlights that the measurement of function over time in response to cancer treatment remains limited in cancer research. When measured at all, it is often measured at only 2 timepoints (eg, at baseline and once after a period of treatment). Increasing the number of serial measurements over time allows for tracking of functional declines, recoveries, and long-term trajectories throughout survivorship.

In the current issue, Stolz et al. (17) exemplify such a longitudinal analysis by measuring self-reported activities of daily living (ADLs), instrumental activities of daily living (IADLs), and mobility limitations monthly in 754 community-living adults aged

70 years or older during the last 5 years before death. Patients who died of cancer demonstrated gradually increasing declines in self-reported mobility, IADLs, and ADLs—generally in that order—after which a drastic terminal decline set in in the last 6 months prior to death. Although this study is a retrospective decedent analysis, which limits prospective prediction of disability trajectories, it demonstrates how serial functional measurement can reveal important insights and implications. One can capture early declines in mobility and higher-order functioning, triggering evaluation for insidious toxicity from cancer treatment, exacerbations from other aging-related deficits, and opportunities for intervening in either cancer or aging-related domains to mitigate and even reverse these functional declines.

In addition to functional tests, blood-based biomarkers reflecting hallmarks of biological aging might help characterize the intrinsic capacity of older cancer survivors (18). At diagnosis, global health status is often a confusing combination of cancer-related deficits that may be reversible and underlying aging-related vulnerabilities that may worsen with treatment. Promising aging biomarkers have been proposed, but few have been studied in cancer survivors (19). In this issue, Yeap et al. (20) measured one such biomarker—leukocyte telomere length (LTL)—in 3608 community-dwelling Australian men with a mean age of 77 years. The authors found an intriguing U-shaped relationship between LTL and both all-cause and cancer-related mortality, suggesting that there may be an optimal length for longevity in cancer survivors. While this work needs to be confirmed, it adds to the literature on how aging biomarkers such as LTL may enhance prognostication alongside clinical variables (21). Like function, measuring aging biomarkers over time throughout survivorship will help refine our understanding of an individual's biological age and how its trajectory is affected by cancer and its therapy. Finally, future basic science and clinical research will reveal the ability of aging biomarkers to distinguish aging-related frailty from cancer-related frailty, with important implications on prognosis and treatment decision making.

Next Steps in Improving Survivorship for Older Adults With Cancer

Reflecting on the studies above, we feel hopeful that progress is accelerating in improving survivorship for older adults with cancer. In line with recommendations from a survivorship conference organized by the Cancer and Aging Research Group, the National Cancer Institute, and the National Institute on Aging (2), we propose the following research priorities:

- Identify valid and feasible assessments of functional status and health-related quality of life that can be used to inform initial treatment decisions and serve as patient-centered outcomes. Measures should be easily integrated into routine care, such as short functional tests, patient-reported outcomes, and, eventually, blood-based biomarkers of aging. Technology such as smartphones and virtual visits could also be leveraged to minimize burden, increase longitudinal measurement, and enhance measurement in patients' homes and communities—settings where function matters the most.
- Conduct observational studies with broad eligibility criteria that include longitudinal analyses of repeated measures and long-term follow-up. Describe the late effects of cancer and cancer therapy, and predictors of patients experiencing declining trajectories in function and quality of life.
- Design and execute interventional studies that investigate the degree to which geriatric assessment-guided interventions prevent or reverse declining function and quality of life in older cancer survivors.
- Examine the efficacy and feasibility of current models of cancer survivorship care for older adults and develop sustainable models. Geriatricians and other aging specialists can play a key role in developing collaborative care models and educational initiatives focused on the interaction of cancer treatment and aging. Just as treatment trials are now being designed by multidisciplinary teams of experts in oncology and aging research, survivorship programs also require a multidisciplinary approach. This collaborative model would foster the implementation of geriatric measures that can identify age-specific complications that arise from cancer treatments (19). Once specific functional outcomes are identified, appropriate clinical pathways and models of care can be developed and integrated into both oncology and primary care.

Together, these priorities will help us to optimize the clinical outcomes that matter most to older patients throughout the cancer survivorship continuum.

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