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Introduction: Personalization of Cancer Care for Older Adults

Noam VanderWalde

Benjamin Movsas
Henry Ford Health, BMOVSAS1@hfhs.org

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Introduction: Personalization of Cancer Care for Older Adults

"The best tunes are played on the oldest fiddles"

Rick Blain (*Casablanca*)

Our population is aging. In June of 2020, the US census bureau published a figure demonstrating the change in the age of our population since 2010 (https://www.census.gov/library/visualizations/2020/comm/a-wave-of-change.html). Every age group from 55 years and above has increased in population, while every age group 20 and lower has decreased. By 2040, it is estimated that > 70% of all patients diagnosed with cancer will be age 65 or older.[1] Yet, old is a relative term. The chronologic definition of old age is and will always be a moving target. Humans, even within the same society, do not all biologically age at the same rate. Thus, a definition of old age which includes the biological changes that lead to physical or functional decline is better suited for the needs of patients and physicians attempting to make complex decisions regarding cancer care. After all, "the number of rotations the earth has made around the sun since a person's birth" does not inherently change that person's suitability for cancer treatment. Just like the beautiful and deep tones of an older fiddle, the depth of experience and wisdom of older adults should be fully appreciated by clinicians.

Yet, an older proverbial fiddle "on the roof" balancing at times precariously due to its potentially more fragile state must be handled with the utmost care and consideration. Indeed, the aging process is often associated with the decline of multiple organ systems over time.[2] This decline can lead to a loss of functional reserve and ability to recover from harm that may occur to those organs. Older adults with functional decline associated with aging may have less tolerance to and thus less benefit from standard cancer therapies, including chemotherapy, immunotherapy, surgery, and/or radiation. Therefore, such "older" patients should not be approached or treated in the same manner as healthier, functionally intact, younger patients. However, how these patients should be treated is still unclear because they are often poorly represented in standard-setting trials, [3] leaving physicians with little data to support their treatment recommendations. This lack of evidence to support optimal treatments for older adult patients can lead to over-treatment in some and under-treatment in others.[4] Unfortunately, the "eye-ball" test of older adults and even basic assessments, such as Karnofsky Performance Status, cannot adequately identify important functional deficits or predict which older adults can tolerate anti-neoplastic therapies.[5,6] Thankfully, over the last couple of decades, the field of geriatric oncology has developed tools to help cancer physicians better identify important clinical variables that can predict important outcomes and allow oncologists to personalize the treatment of older adults with cancer.

Ten years ago, this journal published a special edition on Cancer, Aging, and Comorbidities.[7] Since then, significant changes and improvements have been made in geriatric oncology. In this issue of *Seminars in Radiation Oncology*, entitled "Personalization of Cancer Care For Older Adults", updates in the care of older adults and how these can be translated into oncology now and in the future are featured. The implementation of assessments of older adults with cancers are now being used in multiple settings to help clinicians and their patients make treatment decisions. Surgical oncologists can use these assessments to help decide on the best approaches for resection including who would benefit from robotic or minimally invasive approaches.[8] Medical oncologists can use assessments to predict cytotoxic chemotherapy toxicity and who would benefit from dose-reduced treatments or targeted agents.[9,10] New studies also suggest that intervening on the assessment's findings can reduce toxicity from chemotherapy.[11,12] While this issue will focus on how these assessments can impact the field of radiation oncology, these principles apply across the entire multidisciplinary cancer team, including not only medical and surgical oncologists, but also the important roles of nurses, navigators, psycho-oncologists, physicists, therapists, and so many more.

Radiation oncologists may see a greater portion of older patients who are deemed ineligible for surgery or intensive systemic chemotherapy, due to the potentially lower rate of systemic toxicities from radiotherapy compared to cytotoxic drugs, or general anesthesia. Thus, radiation oncologists must understand how age and the aging process can impact our choices for appropriate care. Radiotherapy is a local and/or regional treatment, thus, the impact that comorbidities

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have on tolerance to radiotherapy may be very different from how they impact surgery or systemic therapy. Moreover, a comorbidity's association with tolerance to radiotherapy will be different depending on the area of the body being irradiated. Due to the daily nature of many of our treatments, a decline in physical function or social function, such as the inability to drive or find transportation, could impact radiation treatments more so than with other fields. At the same time, the daily visits often required for radiotherapy, also allow multiple opportunities for interventions to help reduce possible side effects associated with aging.

The very nature of radiotherapy treatments allows for more personalized treatment for patients. In our image-based planning, radiotherapy is personalized to the anatomy (and at times functional anatomy) of the individual patient. Adaptive radiation planning, including newer techniques such as MR-guided adaptive radiotherapy, can even allow for real-time changes in treatment planning personalized to the patient's "anatomy of the moment".[13] Some have even suggested genome-based adjustments to radiation doses which may allow future radiation oncologists to better estimate the risk and benefit of radiotherapy doses for their patients.[14] The personalized treatment our field already delivers could be made even more appropriate by incorporating functional assessments, comorbidities, quality of life, social factors, and other geriatric principles into our treatment decisions and deliveries. A screening geriatric assessment (GA) (discussed in more detail in the first and last articles), completed before treatment, could help predict life expectancy (eg, eprognosis.ucsf.edu), expected toxicity from chemotherapy,[15] postoperative morbidities,[16] post-radiotherapy quality of life,[17] and could identify social issues including transportation problems. Any of the above, if identified before treatment, can help both clinicians and patients decide on the best treatment options, whether choosing to attempt single modality versus trimodality, palliative intent treatment versus curative intent, or choosing a shorter (hypofractionated or stereotactic) radiotherapy course. As eloquently expressed by Lichtman et al. "[Geriatric assessment] results can be more important than the results of a molecular study or a scan, and the acting on GA information is personalized medicine in its highest form".[18]

In the first review of this issue, Outlaw et al. discuss the history of the field of geriatric oncology and how the GA has evolved over the last decade. Specifically, they review how these assessments are currently being used in clinical trials and several oncology clinics to better inform cancer treatment decisions and to implement interventions that could improve cancer tolerance Multiple geriatric assessment options and their interpretation are detailed as a roadmap to help clinicians implement those assessments in their clinics. In the second review, O'Donovan et al. discuss how radiation oncologists are beginning to implement some of these tools into their clinics and trials. Additionally, they discuss the results of a recently published survey of radiation oncologists demonstrating the continued interest in these assessments, but the need for more knowledge and experience to fully implement them. In the next review, Morris et al, highlight the importance of educating those who work in radiation oncology clinics (therapists, nurses, physicians, etc.) on important geriatric principles to more rapidly and efficiently implement the improvements necessary to upgrade treatments for older adults. In the fourth review, Ludmir et al highlight why obtaining the evidence necessary to improve the care of older adults has been so difficult. For decades, clinical trials (both run by industry and the cooperative groups), have largely disparately accrued younger and healthier patients into trials that set the standards of care for most cancers.[19,20] The authors highlight efforts underway to improve clinical trial designs which will lead to narrowing of the evidence gaps that exist in how to care for older adults with cancer.

In the next set of reviews, we emphasize important updates in the field of radiation oncology specifically, which can be implemented to improve the care of older adults. Tsai et al discuss the treatment of oligometastatic disease and how radiotherapy has evolved to improve the care of older patients with stage IV disease as well as their younger peers. The next review by Germino et. al highlights the use of combined immunotherapy and radiotherapy and specifies ongoing trials of such treatments within older patient populations. The next three mini-reviews all discuss the role of hypofractionation in older adults. The first by Kunkler reviews the role of hypofractionation and ultra-hypofractionation within breast cancer. Edmonston et al, discuss treatment options in patients with GBM and offer ways in which treatment choices could be based on functional assessments. Zhang-Velton and Sanford review the role of shorter radiation courses in patients with GI cancers and offer recommendations on when best to use hypofractionated courses in older adults.

Our last two reviews focus on various aspects regarding the biology of aging and how syndromes associated with aging may impact tolerance to certain anti-neoplastic therapies. Al-Jumalyi et al, specifically discuss biologic mechanisms of both aging and radiotherapy damage and how radiotherapy may accelerate the aging process. In the final review, Extermann and team discuss the potential future of personalized medicine for older adults. By combining biology and potential markers of aging, functional assessments that predict toxicity, patient-reported outcomes, and improvements in Artificial Intelligence (AI), clinicians in the near future will hopefully be able to better predict the true risk and benefits of treatment options for each individual older adult with cancer.

Of course, this issue does not encompass all of the important topics in geriatric oncology. However, we hope that this special edition will encourage oncologists, and radiation oncology teams in particular, to take a more active role in assessing and improving cancer care for older adults. We also hope that in 10 years from now, a new special edition will highlight all of the excellent work done in older adult studies performed in oncology clinics throughout the world. We would like to thank all of the authors who contributed to this edition for their hard work and expertise. We would also like to thank our mentors and mentees who continue to teach us every day. Special thanks to our families for their

continued support and patience. Finally and most importantly, we would like to particularly thank our older cancer patients and let them know that just like the beautiful and deep tones of an older fiddle, the depth of experience and wisdom of age that they share is profoundly inspiring to us.

Noam VanderWalde, MD, MS* and
Benjamin Movsas, MD†
*Department of Radiation Oncology, West Cancer Center and Research Institute in Memphis, TN
†Henry Ford Cancer Institute, Michigan
Address reprint requests to Noam VanderWalde, MD, MS
Department of Radiation Oncology, West Cancer Center and Research Institute in Memphis, TN
E-mail: nvanderwalde@westclinic.com
(N. VanderWalde).

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