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Predictors of Toxicity Among Older Adults with Cancer

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An increasing number of cancer patients are of advanced age as the incidence of cancer increases with age. In this article, the clinical predictors of toxicity that may help in treatment selection are addressed, as well as mitigators of toxicity. The potential of artificial intelligence to enable further progress in the understanding of the interaction of age and tolerance to radiation is reviewed. The final section reviews the literature on patient-related outcomes for older patients.
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KEYWORDS: Radiation oncology; aging and cancer; geriatric oncology; radiation toxicity; CRASH score; radiomics; artificial intelligence; patient reported outcomes

The focus of this article is on radiation toxicities experienced by older patients. Despite radiation oncology advances in conformal targeting, normal tissue is always in the radiation exposure field and normal tissue complications remain a concern. With a focus on aging, the clinical predictors of tolerance are reviewed along with the literature suggesting radiation injury can be reduced pharmacologically. Artificial intelligence using large datasets provides a window into the understanding of the interaction of age and tolerance to radiation and a review is provided. Finally, a summary of the current state-of-the-art regarding patient-related outcomes in older patients is summarized. In summary, a unique perspective of radiation toxicities among older adults with cancer is provided.

Clinical Predictors of Tolerance to Radiation

While an extensive literature exists on predicting side effects of chemotherapy in older patients, much less has been written on radiation therapy. The grading of adverse events from radiation was somewhat late being standardized in the National Cancer Institutes' Common Terminology Criteria for Adverse Events (NCI CTCAE) system. It is only with version 3.0 that it became fully integrated.[1] Beyond the general predictors of radiation toxicity, such as volume, fractionation, and technique, which we will not review here, models are few and not age-specific. Machtay et al analyzed the predictors of late toxicity after Concurrent Chemo-Radiation Therapy (CCRT) in locally advanced head and neck cancers and identified older age, advanced T-stage, and larynx and/or hypopharynx primary site as strong independent risk factors.[2] Ward et al. developed a nomogram to predict late toxicity after reirradiation for head and neck cancers in the context of competing cancer events.[3] They identified 6 predictors of late toxicity: dose of radiation during the first course of treatment, tumor site (oropharynx, hypopharynx, larynx vs others), organ dysfunction, prior surgery, age (with an inverse correlation of 0.997/year), and recurrence vs second primary. Similar nomograms have been developed to predict acute lower gastrointestinal toxicity,[4] late urinary toxicity,[5] and rectal toxicity[6] after prostate cancer radiotherapy.

Some efforts have been made to address the impact of geriatric impairments on toxicity from radiation therapy. One small study assessed whether the G8 screening score was correlated with toxicity of stereotactic radiation for early-stage non-small cell lung cancer. A G8 score ≤14 was correlated with late, but not early, toxicity.[7] Another study assessed whether the Edmonton Frail Scale correlated with toxicity from radiation at

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various sites. No correlation was found.[8] In a larger study, the Vulnerable Elders Survey (VES)-13 score was associated with the inability to complete radiation. Patients with a score > 3 were 2.14 times less likely to complete treatment, and with a score >7, 3.34 times less likely.[9]

Radiation is frequently part of a multimodality treatment plan, sequentially or concomitantly with chemotherapy. Two predictive scores have been developed and validated to predict toxicity from chemotherapy: the Chemotherapy Risk Assessment Scale for High-age patients (CRASH score),[10] and the Cancer and Aging Research Group (CARG) score.[11] These scores combined components of a geriatric assessment and classic oncology predictors. While neither of these scores has been validated for chemoradiation, the CRASH score has a feature that permits its adaptation to such regimens. The CRASH score adapts for the toxicity of the treatment regimen using the MAX2 score.[12] This score is the average of the incidence of the most frequent grade 4 hematologic toxicity and the most frequent grade 3-4 non-hematologic toxicity published about a given regimen. If a chemotherapy regimen has for example 35% of G4 neutropenia and 23% of grade 3-4 diarrhea, the MAX2 score will be 0.29. For a chemoradiation regimen, such as cisplatin and/or etoposide and thoracic 3D/IMRT radiation, the MAX2 score would be 0.235 using a similar approach. If that person had a blood pressure of, 140 on 80, an ECOG PS of 1, a Mini Mental Status of, 28 of 30, a Mini-Nutritional Assessment score of 25, a low normal LDH, and were independent in all IADLs, that person would have a medium low risk of grade 4 hematologic toxicity and a high risk of grade 3-4 non-hematologic toxicity, overall a medium high risk of severe toxicity compared to an average study patient (medium risk) (https://moffitt.org/eforms/crashscoreform/).

To our knowledge, no similar score has been created for older patients undergoing radiation therapy alone. Such scores may have to be modulated according to site of radiation, given the local nature of radiation therapy. However, approaches such as radiomics analyzing tolerance to radiation of healthy tissue might be an avenue along which to progress.

Automation and Modeling for Clinical Decision Support

The significant advances in computational technology over the past 15 years including the availability of ultra-fast computational systems, parallel processing on fast graphics processor units (GPU's) and other architectures, and cloud-based server models have facilitated the automation of workflow processes in radiation oncology. Automation has been shown to be clinically applicable to virtually all elements of the radiotherapy chain, including contouring and/or segmentation of targets and normal tissues on planning images, image registration, treatment planning and dose calculation, treatment plan QA, image-guided delivery, and patient follow-up.[13,14] Benefits of automation encompass facets such as better consistency, increased efficiency and reliability, enhanced quality, higher performance and potential for cost reduction.[13,14] While the automation backbone is powered by high-efficiency computational hardware, the individual clinical workflow processes are implemented by software often driven by machine learning algorithms. Machine learning (ML) refers to the class of computational, data-driven algorithms trained on human behavior from prior experiential data. ML is considered a subset of Artificial Intelligence (AI), the latter which generally encompasses all approaches to emulate human intelligence through the use of machines. Here we will use the AI and ML terms interchangeably. Several researchers have reviewed the role of ML algorithms for automation of the various steps of the clinical workflow, and it is clear that the application of AI in radiation oncology represents a paradigm changing technology.[15-20] Considering that cancer often preferentially afflicts the aging population, the benefits of automation are bound to positively impact clinical workflows and outcomes for older adult patients.

Over the past 5 years or so there has been a significant increase in the application of radiomics-based approaches as imaging biomarkers in cancer treatment,[21] in part because patient imaging is often acquired as a component of minimally-invasive clinical workup. Radiomics is a field that encompasses the extraction of data or features from medical images (CT, MRI, PET, etc.) to define a set of quantifiable imaging patterns that potentially serve as imaging biomarkers of a given endpoint, such as a phenotype or a specific outcome.[22-25] Radiomics-based signatures can be both predictive and prognostic with regard to clinical outcomes and treatment pathways.[26] As such radiomics-based models can be used to provide clinical decision support.[23] Radiomics can be combined with genomics (radiogenomics [23]), clinical factors, and even biological information (eg, assessment of tumor-infiltrating CD8 cells in response to immunotherapies [27]) to enhance the value of decision support models.[15,28] The significant interest in the field of radiomics has indeed been recognized by the National Clinical Trials Network (NCTN).[29]

In the context of non-cancerous illness affecting older adults, radiomics research has centered on applications related to prognostic and predictive modeling of neurocognitive impairment and degeneration in the aging brain tissue related to Alzheimer's disease,[30-32] characterization of stroke from neuroimaging,[33] and age-associated changes in lung tissue.[34] CT-evaluated sarcopenia has been linked to worse outcomes from chemoradiation of head and neck cancer patients.[35] Presently there is limited data on the application of radiomics biomarkers for tumor and normal tissue response specific to older adults with cancer. However, there is significant potential to incorporate imaging signatures relevant to the aging population to build decision support models for personalized treatment.

The utility of radiomics is not without drawbacks. There are several confounding factors related to the impact of image acquisition parameters and image processing on the radiomics features [36,37]; reproducibility of features extracted based on the algorithmic implementation[24]; interpretability of the features associated with clinical outcomes,[24] among others. The International Biomarkers Standards Initiative (IBSI)[24] was formed to standardize the implementation and application of radiomics

algorithms with the goal of enabling consistent results across institutions,[38-41] ultimately to facilitate reliable associations between radiomics signatures and outcomes.

AI algorithms can be used in conjunction with radiomics and other biomarkers to optimize the associations between the radiomics biomarkers and pertinent outcomes.[42] AI algorithms are trained by prior human experience, often in the form of 'ground truth' image data. The accuracy of the AI model is entirely dependent on the number of datasets (sample size) and the availability of properly validated and curated datasets.[16] The lack of big datasets for the training of algorithms can lead to overfitting of the model in situations that are significantly different (varied) from the training datasets.[18] The lack of validated and curated datasets can lead to inaccurate data being used in the training phase; if the data inputs are unreliable then the model will be subsequently trained on inaccurate prior data, thereby limiting the clinical utility of the model.[18] Similarly, imaging biomarkers, such as radiomics rely on large samples of high quality 'big data' in order to build accurate and robust models for clinical decision support. It is likely that the utilization of effective tools such as AI, radiomics, and other imaging biomarkers will become integral instruments for clinical decision support toward improving cancer outcomes in the aging population.

Mitigators of Radiation Injury Among Older Patients

Many older patients take medications that are known mitigators of radiation injury. Medicinal interventions to reduce the harmful effects of ionizing radiation can be classified as pharmacological and non-pharmacological, including exercise, diet, and microbiome. These are areas of intense research because it is generally believed they significantly impact aging, reduce disease, and improve both quality and longevity of life.

Anti-Inflammatory Agents

FDA-approved agents for a host of ailments are under off-label use evaluation in pre-clinical models for their ability to reduce normal tissue injury. The majority of these exhibit anti-inflammatory properties; statins have protected against and mitigated radiation lung injury,[43] angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) have protected against and mitigated radiation lung, kidney, skin, brain, and other organ injury,[44] and metformin has protected against and mitigated radiation injury to the hematopoietic system, GI, and skin.[45,46] It is of note that many older adults with cancer are taking these agents at the time of radiation. The NCI provides guidance for the clinical development of agents that decrease the adverse effects of radiation.[47]

Senolytics

A host of agents known to reduce cellular senescence, so called senolytics, are being developed for their anti-cancer properties have potential to reduce the effects of aging and limit normal tissue damage from chemotherapies and radiation therapies.[48] These include anti-cancer agents that target various molecular pathways such as Bcl-2, PI3K, AKT, HSP-90, p53, mTOR, to name a few. Consider radiation-induced pulmonary fibrosis (PF), for example, a severe late side effect of thoracic RT. Irradiated mice administered an inhibitor of B-cell lymphoma-2 (Bcl-2)/B-cell lymphoma-extra large (BCL-xL) after persistent PF developed reduced type II pneumocyte senescence, and PF was reversed.[49] Promising senolytic approaches with activity in models of older adults include combined Dasatinib and Quercetin, ABT253/Navitoclax and Fisetin pioneered by James Kirkland at Mayo Clinic,[50] Daohong Zhou at The University of Florida at Gainsville,[51] and Johnny Huard at Steadman Philippon Research Institute in Vail, Colorado,[52] to name a few.

Lifestyle Interventions for Radiation-Related Injuries - Exercise

Older individuals who participate in moderate physical activity have increased life expectancy [53,54]; in older subjects, in particular, physical exercise has been found to be beneficial.[54] A review of 13 published studies describing eight different cohorts estimates the benefit of regular physical activity on life expectancy to be between 0.4 to 6.9 years. The UK Biobank longitudinal study of over 490,000 people found an inverse dose-response association between physical activity and mortality.[55] Furthermore, moderate exercise was associated with a longer life expectance in individuals with multimorbidity.[55] Although causality has not been established, individuals who participate in moderate physical activity have longer telomeres [56]; adults with high activity were estimated to have a biologic aging advantage of 9 years over sedentary adults,[56] and exercise favorably lowers senescence markers.[57]

Exercise benefits patients receiving radiotherapy as well, in particular by reducing treatment-related side effects for patients with breast, prostate, rectal, lung, and head and neck cancers.[58] As with exercise and aging, the amount of physical exercise correlates with the benefit.[59]

Lifestyle Interventions for Radiation-Related Injuries - Diet

Nutrition is a key component affecting health of patients receiving radiotherapy,[60,61] although data is lacking for geriatric or specifically for older adult patients. Consumption of red meat, especially processed positively correlates with all-cause mortality whereas that of whole grains, vegetables, fruits, and nuts is beneficial.[62] In animal models, calorie restriction without malnutrition and especially lower protein intake are life-extending factors.[62]

Each of the 5 R's of radiobiology, reoxygenation, DNA repair, radiosensitivity, redistribution in the cell cycle, and repopulation are influenced by metabolism that is affected by diet,[63] hence it is not surprising that diet is an active area of research designed to improve both tumor radiation damage [64,65] and normal tissue response radiation protection.[66,67]

Perhaps not surprisingly, a recent study by Crowder et al.[68] demonstrated that long-term post-radiation head and neck cancer survivors who had symptoms consistent with poor nutrition were associated with decreased functional status and quality of life.

Microbiome

The microbes including bacteria, bacteriophage, fungi, protozoa, and viruses that live inside and on the human body have a profound influence on carcinogenesis and response to therapy.[69] For example, the probiotic Lactobacillus rhamnosus GG (LLG) is being tested to reduce GI injury following irradiation [NCT01839721, NCT03420443].[70] The results of the human studies are consistent with the observation that mice housed in micro-isolators with HEPA-filtered air, acidified water, and autoclaved food and bedding are radiation-resistant compared to the radiation response of mice maintained in a room without such precautions.

Patient Reported Outcomes (PROs)

Patient reported outcomes (PROs) are fundamental to understanding the clinical experiences and symptoms of cancer patients, many of whom are older. PROs have been defined by the US Food and Drug Administration as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else".[71] Examples of validated PRO instruments that include both generic and site-specific cancer modules include the Functional Assessment of Cancer Therapy (FACT) and the European Organization for Research and Treatment of Cancer (EORTC) quality of life (QOL) instruments, among many others.[71] There are many compelling reasons to incorporate PROs into both research and clinical settings. First, PROs have been found to be independent predictors of outcome for cancer patients, including for survival.[72] For example, Movsas et al. found that baseline QOL independently predicted overall survival 5 years later in patients with locally advanced non-small cell lung cancer [73] (3). Similarly, in another lung trial (RTOG 0617), every 10 points higher on the QOL instrument at baseline corresponded to a 10% decreased risk of death.[74] Importantly, geriatric cancer patients have high rates of anxiety and depression, which also correlated with lower survival outcomes.[75] Secondly, PROs can help identify differences in treatment strategies that are clinically meaningful. For example, while RTOG 0617 was not randomized by radiation technology, significantly fewer patients who received intensity modulated RT (vs 3D conformal RT) had a clinically meaningful decline in QOL a full year after treatment.[73] Furthermore, a clinical trial demonstrated that including PROs into the clinical setting can improve the communication between patients and providers.[76]

Perhaps most importantly, randomized data indicates that adding electronic symptom monitoring (to usual care) led to improved QOL, reduced ER visits, and even improved survival.[77,78] In one of these studies,[77] >700 patients with advanced-stage cancer were randomized to reporting 12 common symptoms via tablet or computers versus usual clinical follow-up. Patients in the interventional arm had improved QOL (the primary endpoint), fewer emergency room (ER) visits, and longer median survival (31 vs 26 months, $P = 0.03$). Importantly, they found that these benefits were actually greater for a pre-planned cohort of participants lacking prior computer experience, who overall were significantly older in age (median age 67 vs 60 years in the computer experienced group).[79] Yet, in a subsequent secondary analysis, older patients (>70 years, median age 75) in the electronic symptom management arm still had the primary outcome benefit regarding improved QOL, but not the other benefits (re: ER visits and survival) observed in younger patients.[80] This analysis suggests that there could be differential effects of electronic symptom monitoring based on patient age, though, importantly, the primary endpoint of QOL was not impacted. Indeed, prior studies suggest that older versus younger patients have different supportive care needs.[81] A related key issue with using PROs relates to missing data, which can be even more challenging in older adult patients. By using a HIPAA-compliant web-based electronic reporting system, Movsas et al. demonstrated a significant reduction in missing PRO data compared to using paper forms.[82] The median age in this study was 64 years, suggesting that older patients can also benefit from this approach. More research is needed to develop strategies to further improve and tailor symptom monitoring interventions to better address the personalized symptom care needs of older patients with cancer.

In order to achieve this goal, more studies need to address PROs in the geriatric oncology population. In a recent systematic review of PROs in older patients with breast cancer, van der Plas-Krijgsman et al. found that geriatric parameters (eg, a geriatric assessment or GA) were among key predictors for toxicity and PROs, beyond age and comorbidity.[83] Indeed, PROs were predicted by geriatric measures in >80% of the studies. Yet, only 15% of all studies in this geriatric cancer population addressed PROs.[84] Indeed, the International Society for Geriatric Oncology (SIOG) recommends that PROs be integrated into clinical studies for older cancer patients.[85]. The randomized studies above [77,78] suggest this approach should now be extended to the standard clinical oncology care setting as well. Ultimately, this will lead to better and more individualized treatment decisions and outcomes for older adult patients with cancer.

Fortunately, cancer interventions over time have become more tolerable, convenient, and accessible, which is particularly helpful for older adults with cancer. Radiation has long been a consideration in this regard as it offers a non-invasive treatment option. Mohile et al.[86] reported previously that patient-reported symptoms were similar for older (median age 74) and younger (median age 52) patients receiving radiation. While younger patients reported significantly more pain, nausea, and sleep disturbance, older patients reported more symptom interference with walking. More recently, shorter (hypofractionated) treatment courses have been developed, which provide more convenience. Modern RT

techniques, including MR-guided adaptive RT, provide newer options for older adults with cancer that may have less impact on QOL.[87] Similarly, newer targeted systemic agents and minimally invasive surgical procedures offer more tolerable treatment options for older adults with cancer. Recently, intriguing data is emerging that links PROs to molecular genetic findings.[88] As oncology moves more into the era of personalized medicine using each individual patient's molecular fingerprint, we must still always keep at the forefront the "whole person" (including PROs) when considering "person"-alized treatment options.

Conclusions

Aging affects tolerance to radiation in many ways. Although some efforts have been made to identify clinical predictors of toxicity in older patients, notably the impact of co-morbidities and geriatric syndromes, much work remains to be done to develop integrated prognostic scores comparable to those developed for chemotherapy. Radiomics and artificial intelligence analysis of big datasets may help advance the field. Patient-reported outcomes may bring a key understanding of how radiation toxicities impact the function and the aspects of life that matter most to older patients with cancer.

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