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Narrative review of immunotherapy and radiation therapy in elderly patients

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Abstract: Cancer is primarily a disease of the elderly, but there is a disproportionate lack of data from clinical trials in this population. Oncologists tend to underdiagnose and undertreat geriatric patients with cancer, leading to poor survival outcomes. New therapies or therapeutic combinations such as immunotherapy and stereotactic body radiation therapy (SBRT) can be used in the elderly for better tumor control and survival, with fewer toxicities. The aim of this review is to describe the synergistic effects of immunotherapy and radiation therapy (RT) and to discuss the use of these therapies concurrently and/or sequentially in the elderly. To gain a fuller picture of their elderly patient's health, physicians may also consider incorporating a comprehensive geriatric assessment (CGA) to evaluate their functional capacity, cognition, physical and mental health, and social supports which we will discuss in this review. It is recommended that oncologists use geriatric assessments in their everyday practice to have better insight on their complex elderly patients, therefore providing them a higher quality of care. They should also be incorporated in clinical trials as a way to assess and include more elderly patients in the study. Ultimately, the elderly deserve to be treated with more than their chronological age in mind, and new combination therapies and use of a geriatric assessment can help achieve that.

Keywords: Radiation therapy (RT); stereotactic body radiation therapy (SBRT); immunotherapy; immune checkpoint inhibitors (ICIs); immunotherapy; elderly; older adults

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Introduction

Cancer disproportionately affects individuals in the age 70 years and older, with the elderly population accounting for 80% of all cancer related deaths in the United States (1). As the elderly population in the United States increases, the incidence of cancer in the elderly is also expected to increase from 1.0 million in 2010 to 1.6 million in 2030, as aging is a prominent risk factor for

malignancies (2). There is also an increased risk of mortality due to cancer in the elderly (3). Another challenge of treating cancer in the elderly is the underdiagnosis and undertreatment of their malignancies (4,5). Elderly patients are likely to receive less than the standard of care provided to the younger population, therefore leading to worse outcomes. Older patients were more likely to receive de-intensified treatment and less likely to receive curative treatment, leading to worse comorbidity and decreased

performance status (4-6).

More innovative and focused curative treatment in the elderly are needed to help solve the problem of undertreatment and worse survival outcomes in this population. Immunotherapy and use of immune checkpoint inhibitors (ICIs) show promise in the elderly population, due to the lower rates of severe toxicities when compared to traditional cytotoxic chemotherapy (7). However, as people age, a phenomenon known as immunosenescence, leads to higher susceptibility to cancer, infections, and other autoimmune diseases. Immunosenescence causes a shift in the immune system to a pro-inflammatory phenotype via production of pro-inflammatory cytokines, which can lead to hyper-inflammatory states (8). The direct impact of immunotherapy in the elderly is largely unknown, but data from multiple trials have shown that ICIs are still highly efficacious in this population, even if there is a higher risk of toxicity when compared to younger patients (9,10).

In addition to increased use of immunotherapy in the elderly, radiation therapy (RT) should be considered for this population. RT has been shown to be effective and safe, while providing good local control and low toxicity rates. It can be used as a primary treatment for local control or as palliative treatment to preserve quality of life (QoL) and improve survival. New RT techniques such as brachytherapy and stereotactic body radiotherapy (SBRT) allow for more specialized treatment of cancer in the elderly, as they apply high doses of radiation locally with maximum preservation of nearby normal structures, all within a short total treatment time (11-13). However, clinicians still need to be cautious due to the increased sensitivity of the elderly to radiation or combined chemoradiation toxicities and other treatment related burdens (14). We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2637>).

Methods

An analysis of the medical literature from peer-reviewed journals was conducted from 1970 to 2020 of the PubMed database to retrieve a comprehensive set of relevant articles. The search strategy was developed based on National Library of Medicine® Medical Subject Headings (MeSH®) with addition of subject-specific keywords. The literature was reviewed for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of assessments.

Combining immunotherapy and RT

Immune stimulating effects

The synergistic effects of combining immunotherapy and RT were first described in the 1970s (15). RT has been shown to prime the antitumor response, and this reaction combined with immunotherapies can unleash a more powerful antitumor immune response (16). Immunostimulatory effects of RT include increased recruitment and action of CD8+ T cells and dendritic cells (DC) and increased activation of pro-death signaling in tumor cells through increased expression of major histocompatibility complex (MHC) class I and FAS (17). Lugade *et al.* showed that RT of melanoma tumors in mice models increased the number of T cells that secreted interferon- γ (IFN- γ) and proceeded to exhibit lytic activity. They showed that a single dose radiation treatment resulted in a 3-fold increase in the activated T cell hybridoma B3Z. They proposed that the RT upregulated the molecule vascular cell adhesion protein 1 (VCAM-1) to create a tumor microenvironment that allowed for increased infiltration and killing of tumors by tumor antigen reactive CD8+ T cells (18). Gupta *et al.* found that the efficacy of a 10 Gy dose of RT depends largely on the subsequent activation of DCs and CD8+ T cells. They found that this activation of DCs was crucial to tumor control, rather than the amount of antigen presented by tumor cells (19). Other studies have demonstrated the stimulatory effects of RT on CD8+ T cells and DCs (20-24).

In addition to the increased activation of CD8+ T cells and DCs, the combination of RT and immunotherapy also increases presentation of MHC class I and the FAS receptor, leading to increased killing of tumor cells. The cell models of Reits *et al.* showed a dose-dependent increase in MHC class I expression when exposed to RT, through increased proteasome and mTOR kinase activity, resulting in an increase in intracellular peptides available for surveillance by CD8+ T cells (25). RT also stimulates the immune system through increased presentation of FAS and other tumor antigens, activating the apoptotic pathway. Chakraborty *et al.* found that RT enhanced FAS expression in colon carcinoma cell models and mice models. The FAS/FAS-L pathway is the primary pathway for cytotoxic T cell killing of cells. The upregulated FAS was biologically active and upregulation was maintained for over 96 hours. They found that localized RT significantly increased tumor rejection by cytotoxic T cells. In addition, *in vivo* mice studies showed the enhanced efficacy of cytotoxic T cells when exposed

to RT. The 50% of mice treated with RT and cytotoxic T lymphocyte adoptive transfer resolved their tumor mass and were tumor free for 40 days (26). Lastly, several studies have also demonstrated these effects (27-32).

Immune inhibitory effects

In contrast to its stimulatory effects on the immune system, RT also has inhibitory effects such as increasing the expression of immune checkpoint molecules and increasing expression of regulatory T cells. Immune checkpoint molecules such as programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) are normally expressed by normal, healthy cells to stop unnecessary apoptosis from cytotoxic T cells but can be exploited by tumor cells to evade the immune system (33). Park *et al.* found that knocking out PD-L1 in mice resulted in increased antitumor response and survival when compared to PD-L1 wild-type mice after SBRT. Combined, SBRT + PD-L1 blockade, was more effective than SBRT alone, leading to almost complete regression of the primary tumor, and 66% reduction of a secondary tumor, which was defined as disease outside of the radiation field (34). Similar synergistic effects have been shown when combining RT and anti-CTLA-4 antibodies. CTLA-4 acts similarly to PD-L1 by suppressing immune responses via negative signaling pathways and inhibition of activating signaling. Ruocco *et al.* found in mouse models that the combination of anti-CTLA-4 antibodies and RT increased MHC class I cytotoxic T lymphocyte killing. Combined, RT and anti-CTLA-4 antibodies successfully controlled the primary tumor and also reduced the non-irradiated metastases of the mice (35). Many studies have demonstrated similar synergism of RT with anti-PD-L1 or anti-CTLA-4 antibodies (27,34-43).

In addition to its effects on ICIs such as PD-L1 and CTLA-4, RT also increases immune system inhibition by increasing the regulatory T cell population. Regulatory T cells modulate effector T cells by producing immunosuppressive cytokines like IL-10 and TGF- β . Tumor cells can recruit peripheral regulatory T cells and induce the conversion of CD4+ T cells into regulatory T cells within the tumor, therefore inhibiting the proliferation and apoptotic activity of cytotoxic T cells. Beauford *et al.* found that human natural regulatory T cells and induced regulatory T cells are more resistant to RT than CD4+ T cells. However, the surviving regulatory T cells had reduced capability to decrease the proliferation of CD8+ T cells.

This may be due to the decreased expression of FoxP3 after RT, due to the altered gene methylation that irradiation causes. Furthermore, RT also modulates the expression of other proteins associated with regulatory T cells, such as CD25, CD73, and LAG-3. CD25 expression is regulated by FoxP3 and was decreased with RT. CD73 expression increased with RT, and Beauford *et al.* hypothesized this was due to an increase in TGF- β , although another unknown mechanism may also be involved, since CD39, another protein sensitive to TGF- β , was not increased. Finally, LAG-3 expression was significantly increased after exposure to RT. LAG-3 expression on regulatory T cells has been shown to confer greater suppressive capacity, but the results of these experiments showed the opposite, indicating that other signals from proteins such as MHC class II from other immune cells are needed to maximize the suppressive capability of LAG-3+ regulatory T cells (44). Although research on the effects of RT on regulatory T cells is controversial and can show different results, the resistance of regulatory T cells to RT has been demonstrated in several other studies (45-48).

RT and immunotherapy in the elderly

Immunotherapy in the elderly

While the use of immunotherapy has increased in recent times because of its high efficacy and low toxicity compared to cytotoxic chemotherapy, the use of immunotherapy in the elderly has not been studied well compared to their younger counterparts. Elderly adults are under-represented in clinical trials, and because their immune system undergoes immunosenescence, it is hard to extrapolate results of studies and clinical trials of younger patients to an older population. Hallmarks of immunosenescence include a lower number of naive CD8+ and CD4+ T cells in the peripheral blood, likely due to depletion of naive T cells by a lifetime's exposure to immune pathogens (49). In addition, the number of DCs decline, while the amount of mature, differentiated CD8+ T cells increases with age. This leads to a decrease in T cell function, which can cause an impaired response to ICIs (50). Immunosenescence is thought to be associated with the increased prevalence of cancer and other age-related diseases in the elderly population. Another phenomenon known as "inflamm-aging" occurs due to increased amounts of inflammatory cytokines caused by immunosenescence (9,51).

Many ICIs targeting CTLA-4, PD-1, or PD-L1 have

been approved for the treatment of metastatic melanoma, advanced non-small cell lung cancer (NSCLC), renal cell cancer (RCC), and head and neck cancer with agents like pembrolizumab and nivolumab (52,53). ICIs enhance the body's immune response against tumor cells but can also lead to immune-related adverse events (IRAEs), which are caused by activated T cells infiltrating normal tissues, made more severe by blocking immune checkpoints (54). While serious IRAEs are rare (<1%), they may be more challenging to treat in the elderly due to age-associated comorbidities and reduced functional reserve (51). In several clinical trials, there have been no significant difference in the incidence of IRAEs between patients >65 and <65 years. An overview of toxicities of ICIs in elderly patients by Alkharabsheh *et al.* generally saw no overall difference in safety between young and elderly patients in the KEYNOTE and Checkmate trials, and other trials testing atezolizumab or durvalumab (55-61). However, retrospective data from Memorial Sloan Kettering Cancer Center showed higher rates of discontinuation and increased IRAEs in melanoma patients over 80 years of age being treated with ICIs (55). A meta-analysis of nine randomized controlled trials by Nishijima *et al.* showed improved overall survival (OS) and progression free survival (PFS) in younger and older patients treated with ICIs. However, for patients ≥ 75 years of age, there was no OS benefit found when treated with anti-PD-L1 monoclonal antibody (mAb). The authors concluded that this could be due to immunosenescence or lack of enough statistical power to show a significant difference (62).

A retrospective, pooled analysis of the KEYNOTE studies by Nosaki *et al.* found that pembrolizumab, a PD-L1 mAb, was associated with improved OS in patients with NSCLC ≥ 75 years of age when compared to platinum-based chemotherapy [hazard ratio (HR), 0.41, 95% CI: 0.23–0.73] when used as a first line therapy. The KEYNOTE clinical trials studied 2,348 patients with PD-L1+ NSCLC, 264 of who were elderly, defined as ≥ 75 years of age. Treatment with pembrolizumab improved OS for both elderly and younger patients when compared to chemotherapy. Pembrolizumab was also associated with fewer overall treatment-related adverse effects in this population (68.5% *vs.* 94.3%) compared to chemotherapy. The incidence of IRAEs or infusion reactions was higher in elderly patients treated with pembrolizumab compared to chemotherapy (24.8% *vs.* 6.77%), but this incidence of IRAEs in pembrolizumab *vs.* chemotherapy was comparable to that of the younger population (25% *vs.* 5.9%) (63-66). Marur *et al.* performed a similar analysis of four

clinical trials testing ICI use for patients with advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy. A total of 259 out of 2,824 patients enrolled in these trials were elderly (≥ 75 years). Patients receiving anti-PD-1/PD-L1 mAbs had increased OS compared to chemotherapy in all age groups. In addition, grade 3 or 4 treatment-related adverse effects with anti-PD-1/PD-L1 mAbs were less frequent in patients ≥ 75 years (23%) when compared to patients 65–74 years (49%) and <65 years (47%) (67). Overall, this data and other studies support the use of pembrolizumab as monotherapy in elderly patients with PD-L1 >0% NSCLC, as it has a better OS and more favorable safety profile when compared to chemotherapy (63,67-71).

Melanoma, another highly immunogenic cancer like NSCLC, has also been revolutionized by treatment with ICIs. A retrospective study by Betof *et al.* studied 254 patients from two academic centers with metastatic melanoma, treated with anti-PD-L1 or anti-PD-1 mAbs. There were 65 patients aged 65–74 and 47 patients ≥ 75 years of age. They found that there was no significant difference in the OS, PFS, and some toxicities such as colitis, hepatitis, and pneumonitis between the older and younger patient populations. The incidence of other toxicities, including arthritis and thyroiditis were higher in patients aged 65–74 years and ≥ 75 years, respectively. Arthritis was the only significantly increased immunotoxicity in the elderly (10.8%, $P=0.02$) (72). Cybulska-Stopa *et al.* studied 318 patients with non-resectable or metastatic melanoma treated with anti-CTLA-4 and/or anti-PD-1 mAbs. Eighty-two patients ≥ 70 years were included in the study, and comorbidities including hypertension, cardiovascular disease, and diabetes were present in 84% of patients ≥ 70 years of age. Cybulska-Stopa *et al.* found very similar results to Betof *et al.*, with no significant difference in 2-year OS or PFS, and toxicities between patients aged <70 and >70 years. Additionally, the presence of comorbidities in patients ≥ 70 years of age was not significantly associated with an increased risk of toxicity ($P=0.790$) (73). Overall, the results of these studies and more show that the use of ICIs should not be limited in the elderly, even those with comorbidities, but close monitoring should be used in these patients regardless (72-77).

RT in the elderly

RT is a primary component in the treatment of elderly cancer patients with solid tumors and is a potentially

curative option for older patients unable to undergo surgery. Advances to the field allowing for lower toxicity and increased efficacy have been made, allowing elderly patients to more easily undergo RT. However, elderly patients are underrepresented in randomized clinical trials for RT, similar to their previously discussed underrepresentation with immunotherapies. More studies focused specifically on this population would be beneficial for extrapolating data from trials into the actual patient population (78). Additionally, oncologists may exhibit unconscious bias against the elderly and can be more reluctant to treat an older cancer patient aggressively because of their age (79). However, with modern advancements such as SBRT and brachytherapy, curative treatment for elderly patients may be feasible, even if they have multiple comorbidities or frailty that excludes surgery or chemotherapy (13). Therefore, the use of RT should not be discounted in the elderly and has the potential to be more than a palliative option.

As with all other cancer therapies, RT does not come without toxicities. RT can cause acute or late radiation toxicity that can affect treatment plans and outcomes. Acute toxicity is due to damage to rapidly self-proliferating tissues such as skin or mucosa and normally appears 2–3 weeks after starting treatment. The damage can force treatment to stop to allow the tissue to recover, but this pause can allow for the accelerated proliferation of cancer cells, decreasing the likelihood of good local control. On the other hand, late toxicity is caused by damage to tissues that turn over more slowly, such as vascular and connective tissue. Late toxicities can appear months to years after RT and can decrease QoL of the patient because of their irreversible and progressive nature. In addition, elderly patients may have decreased functional reserve of their organs, leading to increased toxicity even with low doses of radiation (80,81). Retrospective studies have shown that the tolerance to toxicities such as mucositis is decreased in the elderly when compared to younger patients. The elderly are more vulnerable to toxicities and the complications they can cause, such as dehydration (82,83). In addition, the concomitant addition of chemotherapy to RT leads to increased toxicity in patients ≥ 70 years, leading to increased hospitalizations and worse OS (84). Caution should be used when treating elderly patients, but this does not always call for a less than curative treatment plan.

In patients with NSCLC, SBRT has been shown to be comparable to surgery and is the treatment of choice for elderly patients with multiple comorbidities that exclude

surgery. A review by Nguyen *et al.* concluded that SBRT was well tolerated by elderly patients with NSCLC and resulted in similar survival rates as those of surgery treatment. Comorbidities such as hypertension, diabetes, and renal disease may increase complication rates after surgery, leading to decreased patient survival after surgical resection. The 3-year OS in elderly patients who underwent SBRT ranged from 40.7% to 53%, even in patients with high Charlson comorbidity grades. SBRT in elderly patients achieved excellent local control, ranging from 83% to 100% with minimal morbidity, and low occurrence of serious toxicities (2.1% to 10%). In comparison, with surgical resection, 44% of patients had a grade 3 complication and one patient died from surgical complications (85). A retrospective study by Takeda *et al.* included 109 patients ≥ 80 years with NSCLC who were all treated with SBRT. The 1-year OS was 95.0% and the 3-year OS was 53.7% for all patients. After one month of SBRT, 90 patients experienced grade 0–1 radiation pneumonitis, 13 patients grade 2, 4 patients grade 3, 0 patients grade 4, and 1 patient grade 5. After SBRT, QoL was maintained, and emotional functioning was improved, whereas QoL worsened after surgery (86). Several studies report similar findings regarding the better or comparable outcomes of SBRT against surgery in elderly patients with NSCLC (87–92).

Head and neck squamous cell carcinoma (HNSCC) is another cancer frequently treated with RT. Haehl *et al.* analyzed 246 patients ≥ 65 years of age with HNSCC who received chemoradiotherapy or RT alone. Out of these patients, 166 underwent definitive RT and the other 80 adjuvant chemoradiotherapy. Patients aged 65–74 years had significantly better OS when treated with concomitant chemoradiotherapy, although the data may be skewed due to the low number of patients ≥ 75 years undergoing chemoradiotherapy. Additionally, this study reported 56.1% of patients reporting grade 3/4 toxicities (93). Another study by Sommers *et al.* described 674 patients with HNSCC treated with definitive RT, in which elderly patients had worse OS than their younger counterparts. The worse survival outcomes were mainly a result of increased non-cancer-related mortality and comorbidities (94). However, Bonomo *et al.* found that a hypofractionated radiation schedule provides good clinical benefit with low toxicity in elderly patients with locally advanced HNSCC. These patients were unable to undergo potentially curative adjuvant chemoradiotherapy or high-dose RT due to their frailty and comorbidities, therefore a hypofractionated RT schedule worked best for them (95).

For patients able to tolerate combined chemoradiotherapy, Belgioia *et al.* recommends they be treated with this method, due to better loco-regional control rates when compared to patients treated with RT only. When RT is used alone, an average weekly radiation dose >9.236 Gy is recommended for the elderly in order to improve local control of the tumor (96). Additionally, a study by Amini *et al.* found increased OS for HNSCC patients ≤81 years with low comorbidity scores and T1–2/N2–3 or T3–4/N0–3 disease, when treated with concurrent chemoradiation, compared to RT alone. Patients who were older than 81, who had T1–2/N1 and Charlson-Deyo comorbidity score 0–1 (CD0–1) disease, or who had T3–4/N1+ and CD1+ disease did not have increased survival with chemoradiation. Elderly patients able to tolerate chemoradiation or who have disease receptive to it should be treated this way for increased OS and better tumor local control (97). Overall, RT is a good choice for elderly patients, especially those with increased frailty or many comorbidities. When treating the elderly with RT, a balance between caution and aggression is needed for them to maintain their QoL while positively affecting survival outcomes.

Combining immunotherapy and RT in the elderly

The combination of immunotherapy and RT has been well studied in clinical trials and is a good option for younger populations but is not well studied in the elderly. The combination allows for increased immune activation because ICIs can combat the immune suppressive qualities of RT, as discussed previously. When treating older patients with combination therapies, there is concern for increased risk of toxicity compared to treatment with single therapies, due to their decreased functional capacity and increased comorbidities (98). However, the combination could be used to maximize the efficacy of each arm of treatment in order to achieve a curative or therapeutic outcome, rather than a palliative one (16). In particular, the combination of SBRT and targeted immunotherapy has been shown to improve disease control rates in oligometastatic disease (99). Therefore, if patients are able to tolerate the combination of immunotherapy + RT, this treatment can be crucial to overcoming tumor immunoresistance and aid in patient survival (100).

A comprehensive review by Belgioia *et al.* describes several studies in which elderly patients were treated with RT and targeted therapy or immunotherapy concomitantly or sequentially. The review focused more on targeted

therapies, but did look at studies where ICIs such as ipilimumab (anti-CTLA-4) and pembrolizumab (anti-PD-1) were combined with RT. The ipilimumab + RT combination was mainly used for elderly patients with metastatic or advanced melanoma, NSCLC, or castration-resistant prostate cancer. In these groups, RT and ipilimumab combined improved outcomes with no increased toxicities. Melanoma patients with brain metastases had comparable survival with patients without brain metastases when treated with ipilimumab and SBRT. The combination was also tolerated well in NSCLC and prostate cancer patients (98).

Belgioia *et al.* also looked at pembrolizumab, an anti-PD-1 therapy, combined with RT in elderly patients with NSCLC and unresectable oral cavity squamous cell carcinoma (OCSCC). In NSCLC, pembrolizumab + RT lead to a significantly longer OS and PFS with a slightly higher risk of pneumonitis according to case reports. A case report of an elderly women with OCSCC suggests that the synergistic effect of pembrolizumab and RT lead to the excellent clinical response of her unresectable recurrent cancer (98). In addition, a case report by Lazzari *et al.* describes an elderly patient with refractory advanced NSCLC who achieved complete remission after being treated with nivolumab (anti-PD-1) after a course of RT. The patient was first treated with cisplatin and vinorelbine chemotherapy, which resulted in the disappearance of two pulmonary nodules, with a third nodule having increased in size. The growing third nodule received consolidative RT with nivolumab monotherapy, which resulted in complete resolution of the pulmonary lesion and was well tolerated, with pruritus as the main side effect (100). The study is an example of combination RT and immunotherapy in patients with oligoprogressive disease and ongoing studies are currently evaluating this clinical scenario.

Another type of immunotherapy + RT combination therapy that has been studied in the elderly is adoptive cytokine-induced killer cell (CIK) or DC therapy with RT. In a study by Yan *et al.*, 68 elderly patients with esophageal carcinoma were randomized into a control group that received RT only or DC-CIK immunotherapy + RT. They found a significant increase in treatment efficacy of the combination immunotherapy + RT. The patients in the study group had better complete and partial control, as well as better stability of the cancer and less tumor progression. The objective response rate in the study group and the control group was 41.2% and 29.4% respectively, and the disease control rate was 85.3% and 61.7% respectively. The control group had higher rates of locoregional and distant

progression, though this was not statistically significant. Toxicities varied between the two groups, with the study group reporting significantly more fever, overexcitation, and insomnia, and the control group reporting significantly more severe bone marrow suppression. Digestive tract reactions and tracheitis were observed in both groups. The study concludes that DC-CIK immunotherapy and IMRT is safe and effective in treating elderly patients with esophageal carcinoma (101). Overall, these studies support the combination of immunotherapy and RT in the elderly, but more higher powered studies are need for our older adults.

Using geriatric assessments

The increased incidence of cancer in the elderly is disproportionate to the paucity of data and clinical trials focused on treating cancer in this multifaceted population. Clinicians may have trouble treating the elderly because of this lack of data or because of inadequate training and understanding of the elderly, leading to undertreatment and potentially worse outcomes (14). A comprehensive geriatric assessment (CGA) can help physicians better understand the complexity of older patients. A CGA is a multidisciplinary evaluation of an elderly patient's functional status, medical comorbidities, cognition, psychological state, nutritional status, and social support. The CGA is able to predict survival, toxicities, morbidity, and mortality of an elderly cancer patient, and incorporating it into the general practice of treating elderly cancer patients can guide treatment plans to improve survival and QoL outcomes (102). The elderly population's representation in clinical trials is biased due to selection of relatively healthy elderly individuals to meet clinical trial inclusion criteria. Clinical trials generally require their selected patients to have little to no comorbidities, which is not representative of the general elderly population (69,78). Clinical trials should consider using assessments such as the CGA to more properly measure whether or not an elderly person is able to be included in the study, as our current performance scores are not felt to properly capture the true functional status of our older adult patients. Furthermore, a CGA can provide additional endpoints for clinical trials such as QoL and functional independence to expand the breadth of information the trial provides (102).

It is important for current physicians to be able to use tools such as the CGA. A study by Morris *et al.* of radiation oncologist trainees identified knowledge gaps regarding

geriatric oncology, with 91.8% of respondents never receiving specific geriatric oncology training, and 80.3% of trainees rarely or never using geriatric assessment tools. Due to this lack of knowledge, trainees had little confidence in their ability to manage complex issues in the elderly. The 85.3% of trainees agreed or strongly agreed that they needed more geriatric oncology specific training (103). Future physicians should be trained to use assessments such as the CGA to provide personalized and adequate care for their elderly patients. A CGA is able to identify vulnerabilities or abnormalities in the elderly that are not addressed in routine oncology visits and performance status scores including the European Cooperative Oncology Group (ECOG) and Karnofsky Performance Status (KPS) scores. This helps find areas where interventions can be made outside of oncologic treatment, such as nutrition, social support, and physical therapy (104). In addition, geriatric assessment tools can be used to better identify frailty, an increased vulnerability to negative changes in health status. A study by Kirkhus *et al.* found that a geriatric assessment was better able to identify frailty in older cancer patients than oncologists' clinical judgement of frailty. Therefore, using a geriatric assessment helps oncologists make appropriate treatment plans for their elderly patients (105). In order to provide elderly cancer patients with the highest quality of care, it is recommended that all oncologists use some form of geriatric assessment in their clinical practice and prospective studies including older adults should make CGA a component of the studies.

Conclusions

The elderly continue to be an understudied population despite their increased incidence of cancer and other comorbidities. The revolutionizing combination of RT and immunotherapy may prove to be particularly helpful in this population, due to their combined immune stimulatory effects and relatively tolerable side effect profile. There is some concrete data on the use of RT or immunotherapy separately in the elderly, but a substantial lack of information on the combination of the two in the elderly. A solution to the underrepresentation of this population in clinical trials and other studies is increased use of geriatric assessments by clinicians and researchers. Geriatric assessments help synthesize information such as functional status, comorbidities, and social support in order to help physicians look at elderly patients as more than their chronological age. They help physicians be more aware

of their elderly patients' functional status and give them a clear path to high-quality and appropriate treatments for their patients. Ultimately, the elderly are a complex and heterogeneous population, and should be treated as all cancer patients, with a multidisciplinary approach.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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