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*Editorial*

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# Boosting Response: The Impact of Immune Checkpoint Inhibitors on Radiation Treatment Schedules

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The recent FDA approvals of immunomodulatory drugs such as Nivoluvamab (Opdivo), Pembrolizumab (Keytruda) and Ipilimumab (Yervoy) for treatment of Non-small cell lung cancer (NSCLC) and melanoma have renewed interest in cancer immunotherapy. Initial attempts to activate the immune system to improve anti-tumor immunity by vaccination and/or cytokine treatments failed due to low response rates and high toxicity.[1,2] However, improved knowledge of interactions between tumor cells and the immune system has led to a change in strategy. Recently, it has been shown that tumors activate immune checkpoint pathways which suppress any anti-tumor immune responses.[3] Immune checkpoint inhibitors block these pathways and can evoke the power of cytotoxic $CD8^+$ T lymphocytes to eliminate cancer cells.

The first immune checkpoint inhibitor Ipilimumab, a monoclonal antibody to CTLA-4, was approved by the US FDA in 2011 for the treatment of unresectable or metastatic melanoma and has since shown some efficacy for the treatment of other solid tumors such as lung, head and neck, and sarcomas in combination with standard treatment regimens. CTLA-4 is a surface receptor which inhibits T-cell co-stimulatory signals and prevents cytotoxic T-cell activation. By blocking CTLA-4 signaling, ipilimumab allows activation of anti-tumor $CD8^+$ T-cell responses. The success of ipilimumab led the way for development of other immune checkpoint inhibitors such as Nivoluvamab and Pembrolizumab which both target the PD-1 (programmed death-1) pathway. PD-1 ligands (PD-1L) are released by tumor cells and lead to immunosuppressive effects including reduced $CD8^+$ T-cell proliferation and decreased production of immunostimulatory cytokines.[4] Blocking the PD-1 pathway results in increased activation of effector T cells and increased tumor immunity.

In spite of promising results with these new immunotherapies, many patients do not respond or develop resistance, suggesting the need for combination therapies. Additionally, response to these therapies may be limited to patients who have a pre-existing density of clonal $CD8^+$ T cells.[5] Nonetheless, responses may be improved by optimizing the immunostimulatory effects of standard therapies may to augment immune responses elicited by these agents and improve clinical outcomes.

Radiation has long been known to enhance anti-tumor immunity due to the release of tumor specific antigens from dying tumor cells which stimulate T-cell mediated immune responses. Additionally, radiation has been shown to upregulate many cell surface receptors important for immune activation and regulation. Amplification of immune responses by radiation has been shown in clinical setting but the radiotherapy dose and fractionation regimen has not been well defined. Animal models have demonstrated that the abscopal effect of radiation

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can vary depending on the dose and fractionation scheme, with lower fraction, higher dose treatments eliciting higher $CD8^+$ T-cell responses and reducing numbers of regulatory T-cells ($T_{reg}$).[6]

In Cancer Letters, Gandhi, et al. recently reviewed evidence for optimal dose and fractionation to maximize its effect on the immune system response against tumor cells.[7] In modern radiotherapy, hypofractionation (large dose per fraction) has demonstrated greater tumor dose response, while sparing surrounding normal tissue. This is mainly due to advancement in technology that enables delivery of higher doses to tumor targets within 1-2 mm spatial uncertainty using Stereotactic Body Radiation Therapy (SBRT) with real-time imaging and radiation beam gating. Currently, treatment schedules for SBRT have not been standardized to enhance the abscopal effect. More work is needed to understand the impact of SBRT dose and fractionation schemes on cytotoxic and regulatory T-cells in a clinical setting.

Likewise, the interactions between newly approved immunomodulators and radiation are not clearly understood. A study recently published in *Nature* suggests that dual inhibition of immune checkpoints in combination with radiation therapy can increase response.[8] This study showed a synergistic effect between radiation and anti-CTLA4 therapy. Treatment of tumors with anti-CTLA4 therapy inhibited T-regulatory cells and increased the $CD8^+$ T-cell to $T_{reg}$ ratio, while radiation enhanced the diversity of T-cell receptors to improve antigenic targeting.

However, while the combination of radiation and anti-CTLA-4 therapies produced responses in some patients, a subset of patients developed resistance to therapy. This resistance was shown in animal models of melanoma to be due to radiation induced up regulation of PD-1L, which could overcome the inhibition of regulator T-cells by CTLA-4. Other studies have confirmed the radiation induced up regulation of PD-1L in the tumor microenvironment can be evoked by INFγ produced by T cells following radiation exposure.[9] To maximize the immunostimulatory effect of the radiation response, it is necessary to understand the kinetics of radiation induced immunostimulation and up regulation of immunomodulatory receptors as this may impact further optimization of clinical radiation treatment schedules.

As of this writing, mostly anecdotal clinical data have shown some benefit in combining radiation treatment with immune checkpoint inhibitors to improve response. Previous clinical studies using cytokine therapy to boost anti-tumor immunity showed the effects of the immunostimulatory cytokine IL-2 can be augmented with SBRT in metastatic renal cell carcinoma and melanoma.[10] Patients had over 66% complete or partial response, much higher than historical controls with IL-2 alone. In a case report, Postow, et al. describe a metastatic melanoma patient treated using ipilimumab alone showed no initial response, but once treated with SBRT (9.5Gyx3 fractions), to have tumor regression not only at the SBRT irradiated area but also in the non-irradiated metastatic lesions.[11] The University of Pennsylvania recently started a phase I trial for to combine SBRT followed by 4 cycles of ibilimumab for metastatic melanoma patients.[8] While toxicity was limited, only 18% of patients showed a partial response. Furthermore, stratification by PD-1L expression in the melanoma lesion resulted in significantly higher overall and progression free survival in patients with low PD-1L expression compared to those with high PD-1L expression. This is likely due to radiation induced upregulation of PD-1L as was observed in animal models after radiation, further highlighting the importance of fully understanding the impact of radiation on immunoregulatory pathways. These findings suggest the possibility that a threshold radiation dose can be delivered by SBRT and may enhance immunogenicity, but also caution that a balance must be met between radiation induced immune stimulation and immunosuppression.

New radiation treatment planning tools are needed to model not only the SBRT dose distributions but the impact that it might entail if an immunotherapy regimen is also administered. The question is how can we determine the hypofractionation schedule in a clinical setting when this is likely to be dependent on immune status and tumor characteristics that may be patient specific? New mathematical and physical treatment models, stochastic or deterministic, have been proposed for hypofractionated radiotherapy with concurrent chemotherapy. For example, Ohri, et al. published a paper titled "Can Drugs Enhance Hypofractionated Radiotherapy? A Novel Method for Modeling Radiosensitization Using *in vitro* Data".[12] In traditional practice, the radiotherapy dose regimen starts with calculating the absorbed dose to tissue (in units of Gray (Gy), which is then folded with the generalized linear quadratic (gLQ) model to calculate the biological effective dose or BED or biologically equivalent dose in 2-Gy per fraction (EQD2). This mathematical model implementation with and without radiosensitizing agents was demonstrated. Similar simulation models for SBRT and immunotherapy agents might be beneficial to optimize the dose per fraction prior to initiation of the immunotherapy. Tumor characteristics, as well as levels of circulating regulatory, cytotoxic and memory T cells which can be monitored prior to and over the course of treatment, may also help to guide the SBRT treatment planner. Currently, such models remain in the research domain, but translation to the clinical setting could potentially improve the successes of cancer immunotherapy.

## CONFLICTS OF INTEREST

The authors have no conflicts of interest with this article.

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