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Exploiting the immunomodulatory properties of radiation therapy

After completing this activity, the participant should be better able to:

- Explain the immunomodulatory changes brought on by radiation therapy to a tumor microenvironment
- Differentiate between the immune-stimulatory and immune-suppressive properties of tumor irradiation
- Define the abscopal effect of radiation therapy and in what settings it is observed most commonly
- Describe the available clinical evidence in support of combining immunotherapy and radiation therapy.

Introduction

Radiation therapy (RT) is a classic treatment modality that achieves local control of various solid tumors by targeting a defined field of interest or disease. Hence, it is generally ineffective in controlling widespread disease and has previously had little purpose in this setting beyond palliation. Immunotherapy is an effective systemic treatment for metastatic cancer even though a large proportion of patients do not respond because of the immune-evasive and suppressive properties of cancer.¹ However, accumulating evidence suggests that these two treatment modalities in combination may complement each other's therapeutic impact and offer greater clinical efficacy. The combination of immunotherapy (IMT) and RT takes advantage of the demonstrated immunogenic properties

of RT.^{2,3} Because RT is targeted directly to the tumor, it does not inherently immunocompromise the host. By not surgically removing the tumor, the body retains an antigen depot of dying tumor cells to act as an in situ tumor vaccine. However, the rational combination of IMT and RT in the clinic is still in its early stages, and its use depends on further understanding of the underlying mechanisms and early immunogenic effects that RT has on the tumor microenvironment.

Radiation-induced immunomodulatory changes in the tumor microenvironment

The activation of immune cells during cancer therapy irradiation is increasingly being recognized.⁴ Leukocytes themselves are highly radiation-sensitive and likely die from apoptosis in the irradiated field. Instead, the immune-activating effects of radiation appear to result from tumor antigens released following tumor cell death, which are then relayed to antigen-presenting cells (APCs) and propagated

to activate the immune system. RT also appears to induce changes in the tumor microenvironment that lead to the recruitment of radiation-naïve immune cells from areas outside the radiation field, resulting in an increase in immune cell infiltration and the targeting and killing of tumor cells.⁵

In a recent study at UT Southwestern, we identified neutrophils as one of the key players in mediating early inflammatory changes caused by radiation therapy in the tumor microenvironment.⁶ In this study we showed that after radiation there is a rapid infiltration of neutrophils as the first inflammatory mediator. We further showed that this is a key step because when it is prevented, anti-tumor efficacy and the radiation-caused immune response significantly decrease. We also explored the possibility of increasing neutrophil infiltration using G-CSF (granulocyte-colony stimulating factor) – a well-known drug currently in clinical use to increase neutrophil production – which successfully increased the anti-tumor immune response and thereby the therapeutic efficacy of radiation therapy.

Because RT causes local inflammation with the infiltration of neutrophils, dendritic cells (DCs) are also attracted into the tumor.^{6,7} In vivo studies have shown that radiation induces the release of damage (or danger)-associated molecular patterns (DAMPs) such as HMGB1, HSP, and calreticulin into the extracellular matrix, thereby promoting the recruitment and activation of APCs such as DCs.⁸⁻¹¹ The DCs transport tumor antigens to regional lymph nodes where an adaptive anti-tumor immune response is initiated. The products

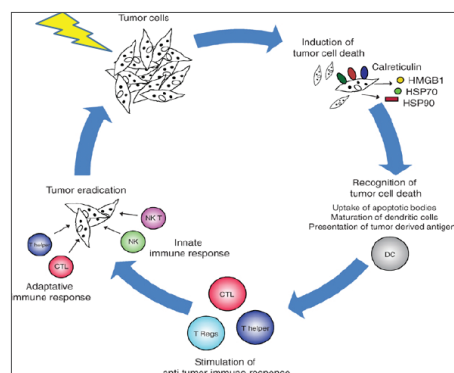


Figure 1: Proposed mechanism of radiation-induced abscopal effect.

of this response (T cells and antibodies) travel back to the primary and metastatic tumor sites to eliminate tumor cells (Figure 1).¹²⁻¹³ Furthermore, RT causes dose-dependent increases in MHC class I tumor neo-antigen presentation by tumor cells,¹⁴ which exposes the tumor's ploy to evade the immune system.¹⁵ This, in conjunction with a demonstrated increase in FAS death receptors on the tumor cell surface in response to radiation, renders tumor cells particularly susceptible to the cytotoxic activity of CD8+ T cells.^{16,17}

The abscopal effect as evidence of radiation-induced anti-tumor immune response

Tumor regression outside of the irradiation field following localized treatment is called the abscopal effect, first described by Robin H. Mole in the 1950s.¹⁸ Until recently, the abscopal effect was poorly understood and regarded as an uncommon phenomenon. But a 2004 preclinical study (Demaria et al.) demonstrated that the abscopal effect was mediated by immune cells when RT inhibited distant, untreated disease in control mice while this effect was absent in immune-deficient nude mice.¹⁹ Likewise, the abscopal effect was eliminated when RT in combination with Flt3-ligand was administered to immunocompromised mice as compared to immunocompetent mice, suggesting that the abscopal effect is immune-mediated.¹⁹ In the clinic, the abscopal effect has been documented by multiple case reports in which RT to one tumor site resulted in a systemic complete response of tumor regression at metastatic sites.²⁰⁻²³

Immune-suppressive properties of radiation therapy

With all these immune-stimulating properties of radiation therapy, one has to wonder why the abscopal effect is not seen more frequently. In fact, the abscopal effect is so rare that it is difficult to see it outside of case reports. This is due to the simultaneous immunosuppressive properties of radiation therapy. While RT increases CD8+ T cells and DCs in the tumor microenvironment,

fractionated RT can subsequently eradicate these cells, leading to tolerance. This is likely the reason the abscopal effect is seen more frequently in the hypofractionated or stereotactic radiation (SABR) dose-fractionation settings. Tumor irradiation upregulates active transforming growth factor beta (TGF- β), which in turn can increase regulatory T cells (T-regs) and inhibit effector T cells.²⁴⁻²⁵ Because T-regs are relatively more radioresistant, their proportional increase has been documented after tumor RT.²⁶⁻²⁸ Increases in bone marrow-derived myeloid cells (MDSC) and immunosuppressive polarization of macrophages contribute to tumor proliferation and recurrence after irradiation.²⁹⁻³² Radiation therapy has also been shown to increase the expression of programmed death ligand 1 (PD-L1) protein on the tumors and monocytes/lymphocytes, which leads to deactivation of cytotoxic T lymphocytes (CTLs) – the so-called “exhausted” CTLs.³³⁻³⁵ Together, these help the tumor escape an immune response.

Radiation and immunotherapy synergy

While it is clear that the immune system plays an active role in the irradiated tumor microenvironment, the activation of a systemic immune response by RT alone usually cannot overcome the threshold of immune-suppression in the tumor microenvironment except in a limited number of instances.³⁶⁻⁴⁰ Therefore, a strategy that counters the immunosuppressive properties of radiation therapy and simultaneously augments its inflammatory properties will see the abscopal effect routinely and reproducibly in the clinic.

In recent years, preclinical studies that combine RT with immunotherapy³⁷⁻⁴¹ have been able to reliably reproduce distant tumor regression outside of the irradiation field using syngeneic mouse models of cancer, thereby validating the combination of RT with immunomodulatory as a promising strategy. In our own syngeneic prostate tumor model, we demonstrated that RT and a Listeria-

PSA vaccine synergize to reduce tumor volume and to generate tumor-specific CD8+ T cells.⁴²

Clinical evidence for the combined use of RT and IMT is also emerging. In a retrospective analysis of 62 patients with stage II-IV breast cancer treated with pre-operative (pre-mastectomy) RT, Konoeda et al. reported an abscopal effect in metastatic lymph nodes in 15 out of 42 cases (35.7 percent) by palpation.²⁰ Biopsy of the lymph nodes revealed a histopathological abscopal effect in 22 out of the 42 cases (52.4 percent). Notably, the patients who experienced the abscopal effect had CD8 and CD4-positive infiltrating lymphocytes around the degenerated cancer cells in the irradiated primary tumor nests. These results show that localized irradiation results in the generation of antitumor immune effector cells and their trafficking to the tumor site.

Wersall et al. reported that non-irradiated lesions in four of 28 patients (14 percent) with primary renal cell carcinoma (RCC) regressed following stereotactic treatment with 96 Gy (12 x 8 Gy).²³ Of the four patients with abscopal response, three patients received nephrectomy and none were noted as having undergone chemotherapy. Notably, one patient after nephrectomy received systemic interleukin-2, whose function is to enhance CTLs. Another recent prospective study reported an abscopal effect in patients with various metastatic solid tumors (44 percent non-small cell lung cancer and 34 percent breast cancer) following chemo-radiation therapy combined with immunotherapy using a cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate dendritic cell maturation.⁴⁵ Patients enrolled in this study were treated with a total dose of 35 Gy in 10 fractions, and an abscopal response occurred in 11 of 41 accrued patients (27 percent). Similarly, a recent retrospective analysis of 21 melanoma patients who received palliative RT after they progressed from receiving the anti-CTLA4 antibody ipilimumab found 52 percent of patients experienced an abscopal response.⁴⁶ Importantly,

median survival of patients with an abscopal response was increased to 22 months compared to nonresponders at 8.3 months. Furthermore, the abscopal effect was primarily observed in patients who experienced a local response, suggesting an effective local response correlates with an abscopal response. Taken together, these studies suggest that the combination of RT with immunotherapy could improve both abscopal response rates and survival.

A recent review of the abscopal effect in medical literature included 23 case reports and 13 preclinical studies.⁴⁷ Studies with concurrent cytotoxic treatment were excluded from analysis, but 11 of the 13 preclinical studies used immune-modulating treatment to achieve the abscopal effect. The median time to induce an abscopal response was five months, and a median progression-free period of 13 months followed the abscopal response. Collectively, these studies suggest combining RT with immunotherapy agents may increase the likelihood of inducing an abscopal effect.

The role of SAbR

Stereotactic ablative body radiation (SAbR) is an emerging treatment paradigm defined as a method to deliver a high dose of radiation to a target within the body, utilizing either a single dose or a small number of fractions with a high degree of precision.⁴⁸ SAbR is utilized against a broad spectrum of tumor types in a variety of body sites due to its excellent safety and efficacy.⁴⁹⁻⁵¹ In fact, the vast majority of preclinical and clinical data on the abscopal effect of RT described in this article come from dose fractionations used in SAbR.^{2,3,7} Because SAbR is a highly focused therapy, the host immune system is not compromised. In addition, as opposed to conventional radiation fields, SAbR spares surrounding lymph nodes vital for the induction of an effective immune response. The antigen-presenting properties and induction of immunogenic cell death at SAbR dose levels are well documented.⁸ In addition to the elimination of bulky primary disease sites producing immune-suppressive factors, SAbR is expected to initiate immunogenic tumor cell death and

tumor-antigen presentation. These processes act as an in-situ tumor vaccination, channeling the non-specific stimulation (i.e., interleukin-2) or inhibition (i.e., anti-PD 1/L1) of IMT.

For physicians and their patients, the promise of SAbR combined with immunotherapy could eventually result in a significant shift in the treatment of metastatic cancer. Currently, this combination treatment is primarily available to patients through clinical trials at academic research institutions. At UT Southwestern, multiple clinical trials are ongoing to evaluate this combination in different tumor settings, including metastatic, castrate-resistant prostate cancer (with Sipuleucel-T), and metastatic renal cell cancer (with interleukin-2 and also with nivolumab).

Through translational studies and careful design of clinical trials we hope to uncover the true immunogenic potential of SAbR and make immunotherapy + SAbR a successful strategy that reliably brings the abscopal effect to routine clinical practice.

Raquibul Hannan, M.D., Ph.D., is Assistant Professor of Radiation Oncology.

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