Stereotactic Body Radiation Therapy and Immunotherapy

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Abstract: Immunotherapy has revolutionized the treatment of various types of cancers in recent years. Since the US Food and Drug Administration approval of the anti–cytotoxic T-lymphocyte–associated antigen 4 agent ipilimumab for late-stage melanoma in 2011, results from multiple clinical trials have proven the benefit of immunotherapy in the treatment of other cancers. However, therapeutic resistance to immunotherapy often develops. This has led investigators to combine immunotherapy with stereotactic body radiation therapy (SBRT) in an attempt to improve outcomes. The benefit of the combination is believed to stem from stimulating and suppressing various immune pathways and is further aided by the abscopal effect, in which tumors respond to radiation therapy even in nonradiated metastatic sites. When combined with immunotherapy, radiation causes the tumor to act much like a vaccine by exposing the tumor antigens to activate the immune response. This article reviews the association between the immune system and cancer, as well as the additional systemic benefit that SBRT can have in patients with advanced-stage malignancies being treated with immunotherapy.

Keywords
Abscopal effect, immunotherapy, stereotactic body radiation therapy

Background

Immunotherapy has achieved good results in patients with various types and stages of malignancies. It has been widely embraced as a therapeutic option given the toxicities of conventional cytotoxic chemotherapy, along with the resistance that ultimately develops with conventional chemotherapy. Immunotherapy is a treatment modality in which the immune system is primed to recognize cancer cells as dangerous, and to eliminate them wherever they are in the organism. Stereotactic body radiation therapy (SBRT), by contrast, targets a specific area. The success of immunotherapy and SBRT has led to studies analyzing the combination of these treatment modalities. The power of the combination is believed to stem from a synergistic effect between immunotherapy and SBRT[1-6] that is further aided by the abscopal effect, in which tumors outside of the radiation field respond to radiation therapy.

Table 1. Evidence for the Relationship Between Cancer and the Immune System

• Downregulation of MHC-I expression in several types of cancer (leading to poor recognition of those cancer cells by the cytotoxic T cells)[32]
• Increased expression of CD47 antigen on tumor cells (protecting them from phagocytosis)
• Increased cancer risk in immunocompromised patients[33-38]
• Increased incidence of certain cancers in patients on immunosuppressive agents[39]

MHC-I, major histocompatibility complex class I.

The Immune System and Its Association With Cancer

The immune system plays an important role in cancer.[7] The downregulation and upregulation of different cellular receptors in the setting of cancer and the increased incidence of cancer in immunosuppressed patients support the association between cancer and immunity (Table 1). The result of the complex interaction between the immune system and cancer cells determines the course of the disease (Figure 1).[8,9] The immune system constantly exerts immune surveillance to detect and try to eliminate cancerous or otherwise abnormal cells (Figure 2). Cancer cells can evade the immune system, however, through manipulation of their own immunogenicity, production of immunosuppressive mediators, and promotion of immunomodulatory cell types. The most widely studied mechanism of immunologic surveillance is the action of T lymphocytes (mainly CD8+ T lymphocytes) and their ability to distinguish between self-antigens and non–self-antigens. This mechanism is referred to as the "immune synapse" (Figure 1).

Principles of Cancer Immunotherapy

Immunotherapy achieves its therapeutic effect by restoring the ability of the immune system to detect and destroy cancer cells.[10] In order to achieve that, it relies on a complex interaction between various types of immune cells (Table 2).[11-13]

Many immunotherapeutic approaches have been studied (Table 3). The major molecules to be successfully used in immunotherapy are the growing class of ligand-receptor pairs, commonly referred to as immune checkpoints. The 2 immune checkpoint receptors that have been most studied, cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1), regulate immune responses at different levels and by different mechanisms. CTLA-4, the first immune checkpoint receptor targeted in melanoma patients, is expressed exclusively on T cells, where it primarily regulates the amplitude of the early stages of T-cell activation. Although CTLA-4 is expressed by activated CD8 killer T cells, the major physiologic impact of this receptor appears to arise through distinct effects on the 2 major subsets of CD4 T cells—downmodulation of helper T-cell activity and enhancement of regulatory T-cell suppressive activity. In contrast to CTLA-4, the major role of PD-1 is to limit the activity of T cells in the peripheral tissues at the time of an inflammatory response to infection and to limit autoimmunity. This translates to a major immune resistance mechanism within the tumor microenvironment.

Table 2. Mechanisms of Action for Various Immune Cells

Immune Cells	Mechanism of Action
CD8+ lymphocytes (cytotoxic T cells)	Initiate the distinction between self-antigens and non–self-antigens, through recognition at the immune synapse
TH1/TH2 subclasses of CD4+ T lymphocytes (helper T cells)	
NK cells	NK cells target cells with low MHC-I expression for destruction Do not require antigen presentation by the MHC-I for cytotoxic activity
FoxP3+ CD25+ CD4+ Tregs, and MDSCs	Inhibit cytotoxic T-lymphocyte activity
Macrophages	M1 macrophages: release IFN-γ and are responsible for phagocytosis
	M2 macrophages: release cytokines such as IL-4, IL-10, and TGF-β

IFN-γ; interferon γ; IL, interleukin; M1 macrophage, classically activated macrophage; M2 macrophage, alternatively activated macrophage; MDSCs, myeloid-derived suppressor cells; MHC-I, major histocompatibility complex class I; NK, natural killer; TGF-β, transforming growth factor β; TH1, type 1 T helper; TH2, type 2 T helper; Tregs, regulatory T cells.

Rationale, Pros, and Cons of Combining Radiotherapy With Immunotherapy

Radiotherapy is an integral part of cancer treatment. The available radiation therapy modalities include SBRT, intensity-modulated radiation therapy, proton radiation, and 3-dimensional conformal radiation therapy. The benefits of combining radiotherapy and immunotherapy have

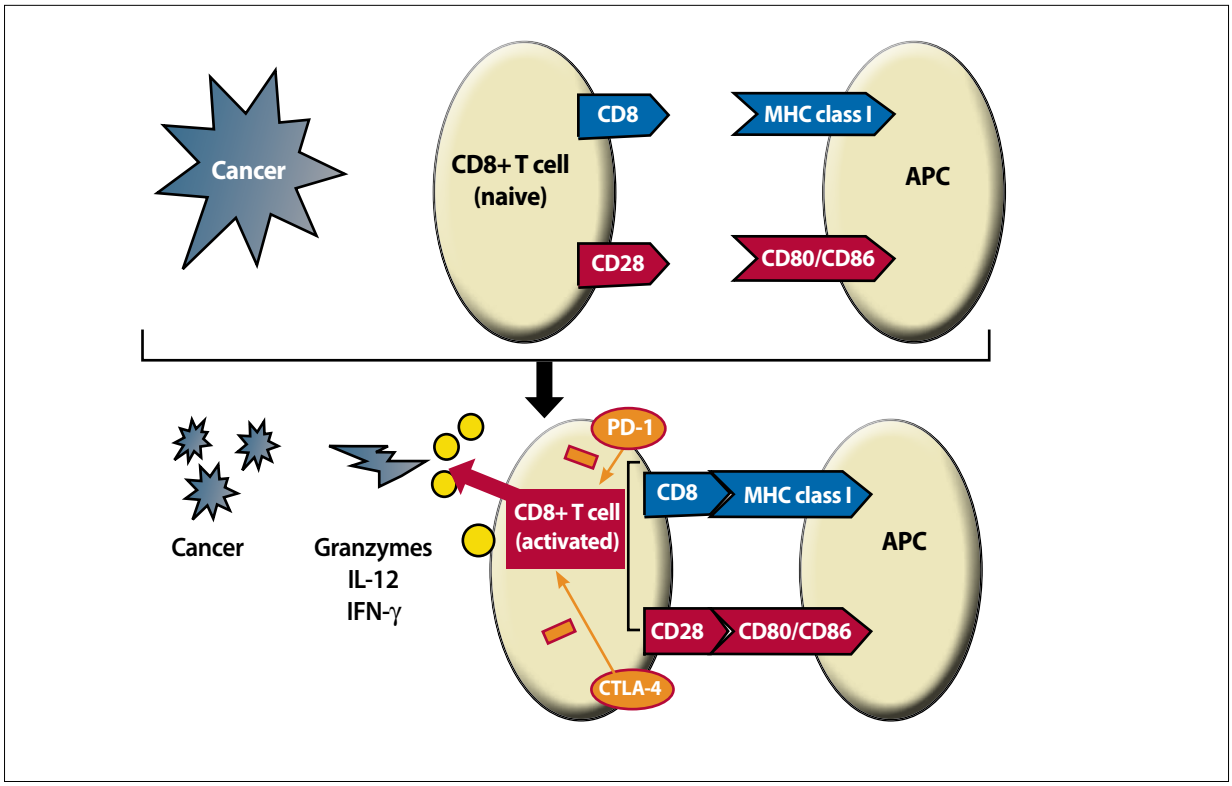

Figure 1. In this illustration of the immune synapse, antigens are presented to the T cells by antigen-presenting cells. The cytotoxic activity of the CD8+ T cell is then regulated by a set of stimulatory receptors (CD28-CD80/CD86 interaction) and inhibitory receptors (CTLA-4 and PD-1).

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; IL, interleukin; IFN-γ, interferon γ; MHC, major histocompatibility complex; PD-1, programmed death 1.

been reported in different cancer types, including head and neck squamous cell carcinoma,[14] metastatic pancreatic cancer,[15] metastatic melanoma,[16] lung cancer,[17] and brain metastases.[18] The benefit of the combination can be attributed to a synergistic effect between immunotherapy and radiotherapy. Immunotherapy works by potentiating the immune response. Instead of radiotherapy providing only local disease control and immunotherapy providing only systemic control, the 2 therapies may enhance each other's effect.[4-6] As a result, researchers have begun to combine immunotherapy with SBRT.

Locally, SBRT can cause direct damage to cancer cells that causes antigen exposure, leading in turn to local and systemic immune system activation.[4,19] It can also stimulate immunogenic cell death and sensitize cancer cells to immunotherapy by promoting the expression of major histocompatibility complex (MHC) class I molecules and other apoptosis-mediating proteins,[20] triggering CD8+ T cells[19] and releasing high mobility group box 1 (HMGB1) from tumor cells upon exposure to x-ray or carbon-ion radiotherapy.[21] SBRT can also induce DNA damage, and the resulting DNA mutations in cells with DNA repair deficiency can increase the burden of neoantigens—which in turn can trigger an immune response.[22]

SBRT can trigger the systemic immune response via radiotherapy-induced microenvironmental changes to tumor cells as well as the surrounding stromal cells.[4] In addition to sensitizing irradiated tumor cells to immunotherapy, radiotherapy can cause the cells to release tumor antigens that prime T cells to attack other tumor cells in the body, including those at distant, nonirradiated sites. In effect, radiotherapy can turn the tumor into a vaccine.

In summary, the current scientific evidence indicates that conventional radiation affects the immunologic profile of tumors in a particular manner which, in turn, might induce beneficial effects at both the local and systemic levels (the abscopal effect). However, the extent of benefit and the amount of toxicity associated with such an approach are not well known.

The Abscopal Effect in Immunotherapy and SBRT

The word abscopal is derived from the Latin *ab* (away

Table 3. Immune-Based Therapeutic Approaches

Type of Immunotherapy		Mechanism of Action	Therapeutic Use
Cytokines	IL-2	At higher doses, IL-2 promotes CD8+ effector T cells and NK cytolytic activity and promotes differentiation of CD4+ cells into TH1 and TH2 subclasses At lower doses, IL-2 promotes expansion of Treg populations (probably owing to the higher affinity of the trimeric IL-2 receptor, also known as CD25) on those cells, and inhibits the formation of TH17 cells implicated in autoimmunity	High-dose IL-2 achieved durable objective responses in a minority of patients with melanoma and renal cell carcinoma
	IFN alfa-2b	Promotes TH1-mediated effector cell responses such as IL-12 secretion via STAT1- and STAT2-mediated downstream signaling events	Adjuvant treatment of high-risk melanoma
	Bacillus Calmette–Guérin	Induces a robust inflammatory response when injected into the bladder	Treatment and secondary prevention of superficial bladder cancer
Checkpoint inhibitors	Anti–CTLA-4 antibodies	Physiologic "brake" on the CD4+ and CD8+ T-cell activation that is triggered by APCs	Melanoma
	Anti–PD-1 antibodies	The PD-1:PD-L1/2 interaction directly inhibits apoptosis of the tumor cell, promotes peripheral effector T cell exhaustion, and promotes conversion of effector T cells to Treg cells	Melanoma, renal cell carcinoma, non–small cell lung cancer, head and neck cancer, urothelial carcinoma, Hodgkin lymphoma, and Merkel cell carcinoma, as well as MSI-H or MMR-D solid tumors
	Anti–PD-L1 antibodies		
Agonists of costimulatory receptors		Studied in preclinical animal models or are in early phases of clinical development	
Manipulated T cells	CAR-T cells	Manipulate patient-specific T cells ex vivo to make them more reactive to specific antigens	Studied most extensively in hematologic malignancies
Oncolytic viruses	Talimogene laherparepvec, also known as T-VEC	Utilizes virus 1 to overexpress GM-CSF, which promotes dendritic cell–mediated antigen presentation	Used in management of localized melanoma recurrence
Vaccines	Sipuleucel-T	An autologous dendritic-cell preparation engineered to target PAP	Has demonstrated an overall survival benefit in men with CRPC

APCs, antigen-presenting cells; CAR, chimeric antigen receptor; CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; GM-CSF, granulocyte-macrophage colony–stimulating factor; IL-2, interleukin 2; MMR-D, mismatch repair deficient; MSI-H; microsatellite instability-high; PAP, prostatic acid phosphatase; PD-1, programmed death 1; PD-L1, programmed death ligand 1; STAT1, signal transducer and activator of transcription 1; STAT2, signal transducer and activator of transcription 2; TH1, type 1 T helper; TH2, type 2 T helper; TH17, type 17 T helper.

from) and *scopos* (target). In oncology, localized radiation has been observed to initiate an antitumor response that kills cancer cells distant from the primary target. This phenomenon of radiotherapy shrinking the tumor locally and inducing an immune response systemically is known as the abscopal effect. By inducing a systemic increase in antigen recognition, radiotherapy may also induce the T cell–mediated inhibition of untreated distant tumors.[23]

A review by Hu and colleagues of 23 clinical cases describing the abscopal effect noted that most instances occurred in immunogenic tumors, such as renal cell carcinoma, melanoma, and hepatocellular carcinoma. However, with the continued development and use of immunotherapy strategies incorporating combinations of targeted immunomodulators and immune checkpoint blockade with radiation, the abscopal effect is becoming increasingly relevant in less-immunogenic tumors, such as breast cancer.[24]

Regarding radiation dose and fractionation effects, a body of literature addresses issues of single-fraction vs

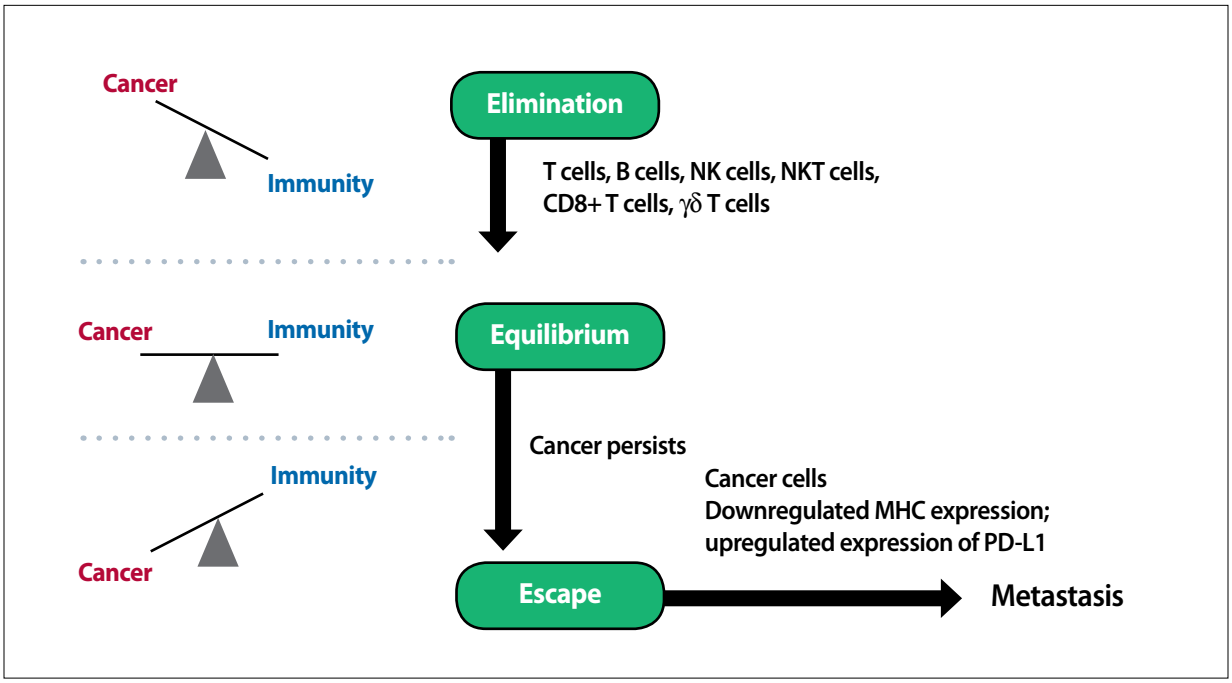

Figure 2. The cancer immunoediting process consists of elimination, equilibrium, and escape. The elimination phase involves targeting and eradicating cancer. In the equilibrium phase, a balance is obtained between progression of cancer and cancer elimination by the immune system. In the escape phase, the cancer overcomes the immune system and metastasizes to the other organs.

MHC, major histocompatibility complex; NK, natural killer; NKT, natural killer T; PD-L1, programmed death ligand 1.

APCs, antigen-presenting cells; CAR, chimeric antigen receptor; CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; GM-CSF, granulocyte-macrophage colony–stimulating factor; IL-2, interleukin 2; MMR-D, mismatch repair deficient; MSI-H; microsatellite instability-high; PAP, prostatic acid phosphatase; PD-1, programmed death 1; PD-L1, programmed death ligand 1; STAT1, signal transducer and activator of transcription 1; STAT2, signal transducer and activator of transcription 2; TH1, type 1 T helper; TH2, type 2 T helper; TH17, type 17 T helper.

multifraction radiation, and whether a dose threshold exists for enhancing immune responses. Both preclinical and clinical reports have demonstrated improved outcomes using single-fraction vs multifraction radiation doses, as well as hypofractionated SBRT dosing vs conventional daily dosing.[25]

The abscopal effect is believed to arise from the capability of local radiation to elicit systemic immune effects that control the nonirradiated tumor burden. In the tumor microenvironment, radiation acts as an immune modulator through several mechanisms. Localized radiation induces cell death and release of immunogenic factors via a process called "immunogenic cell death," which subsequently triggers the release of a number of endogenous damage–associated molecules (calreticulin, high-mobility group box 1 protein, and adenosine triphosphate) that contribute to the priming of the immune system by triggering dendritic cells, resulting in improved antigen presentation to T cells.[26]

Concerns Over the Combination of Immunotherapy and SBRT

The main concern with using combined modality treatments in general is overlapping toxicities. Patients treated with immune checkpoint inhibitors may develop immune-related adverse events, such as fatigue, rash, skin disorders, colitis, and gastrointestinal events.[27,28] When combined with SBRT, the side effects of immunotherapy might be significantly elevated given the potentiating effect that SBRT has on immunotherapy. One retrospective study has shown that adverse events were increased when immunotherapies were combined with radiotherapy for brain metastases.[29] The increased toxicity from the combined modality treatment could stem from the fact that SBRT can expose tumor-specific and nontumor-specific antigens to the immune system. Some of the nontumor-specific antigens might prime autoreactive T cells, which attack and damage normal tissues if not properly negatively selected.[30]

Conclusion

When SBRT is given with immunotherapy, the immune cells can orchestrate an inflammatory environment that may function to inhibit cancer growth both locally and systemically.[31]

The benefit of combining radiotherapy and immunotherapy derives from a complex synergistic interaction between radiotherapy and the immune system.[4] The ability to increase tumor antigen presentation also makes radiotherapy a promising modality in combination with chimeric antigen receptor T-cell therapies.

These findings warrant preclinical studies to investigate the biological mechanisms underlying the increased toxicity, and to identify potential methods to lower such risks. Future prospective clinical studies are needed to improve our understanding of the benefits and risks associated with such combinations.

Disclosures

Drs Khalife, Shahid, Dabney, and Phan have no disclosures to report.

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