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COMBINING IMMUNOTHERAPY WITH RADIATION THERAPY TO INDUCE THE ABSCOPAL RESPONSE: WHAT CLINICAL AND TREATMENT VARIABLES MATTER?

Description

This review article identifies demographic, clinical, and treatment variables associated with the abscopal effect—the phenomenon in which radiation induces a regression of tumor cells outside the field of irradiation. Authors describe the current state of knowledge regarding these variables and examine research on the influence of tumor type, patient's immune system, overall tumor burden, and radiation therapy parameters on the abscopal effect.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the general mechanism of the abscopal effect and why combining radiation with immunotherapy may be beneficial.
2. Understand the types of cancers that are more immunogenic and could benefit from combining radiation with immunotherapy.
3. Update practices based on current literature regarding the optimal radiation dose, fractionation schedule, and timing in relation to immunotherapy associated with improved outcomes.

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Combining immunotherapy with radiation therapy to induce the abscopal response: What clinical and treatment variables matter?

Jason Liu, BS; Heath B. Mackley MD, FACRO

Ionizing radiation has been used for over a century to treat cancer. Historically, radiation was only thought to improve the local control of cancer. However, a growing body of evidence shows that radiation may induce a regression of tumor cells outside the field of irradiation, a phenomenon known as the abscopal effect. This phenomenon was first described by R.H. Mole in 1953.[1] While the mechanism remains unclear, the systemic effect of radiation therapy is believed to be immune related.[2-5] It is believed that the radiation damage induced in the tumor cell causes the release of damage-associated molecular patterns (DAMPs) that serve to immunize the host.[6-10] This can result in the widespread activation of immune effector cells, which can then attack tumor cells distant to the irradiated target.[11-15]

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While the number of case reports documenting the abscopal response is growing, the abscopal response remains rare and difficult to reproduce clinically with radiation therapy alone. Combining immunotherapy with radiation therapy, however, seems promising for bringing out this rare clinical event. Immunotherapy bolsters the host's immune system, examples of which include cytokine therapy, adoptive cell transfer, and the new generation of immune checkpoint inhibitors (ICIs). The two major classes of ICIs include PD-1–PD-L1 inhibitors (pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab) and CTLA-4 inhibitors (ipilimumab and tremelimumab).

An exciting area of research in radioimmunotherapy is identifying what demographic, clinical, and treatment variables are associated with the abscopal response. Here, we review the current state of knowledge regarding these variables and identify areas requiring further investigation.

Abscopal Response Defined

In the literature, an abscopal effect is defined as a phenomenon in which localized treatment of a tumor causes shrinking not only of the treated tumor, but also of tumors outside the scope of the localized treatment. An abscopal effect may be either partial or complete. For purposes of our review, we define an abscopal *response* as a complete response resulting from the abscopal *effect*.

It is difficult to know whether a complete response after radiation and immunotherapy is due to the abscopal response or due to the activity of immunotherapy alone. However, there is evidence that the complete response rate is higher with radiation and immunotherapy than immunotherapy alone, which suggests that a complete response is due to the abscopal effect in patients treated

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with both radiation and immunotherapy.[16-21] A prospective trial in patients with metastatic melanoma treated with radiation and anti-CTLA-4 found the complete response rate to be 13.6%[18] compared to a 1.5% complete response rate for patients with metastatic melanoma treated with anti-CTLA-4 only.[22] While a fraction of complete responses in patients treated with radiation and immunotherapy may be attributed to immunotherapy alone, the majority of complete responses appear related to the abscopal effect.

Influence of Tumor Type

Tumors are complex environments that contain cancer cells as well as stromal and immune infiltrates. Tumor-infiltrating cells can demonstrate either tumor-suppressive or tumor-promoting effects depending on cell type. Regulatory T-cells and tumor-associated macrophages have been associated with pro-tumor functions, whereas $CD8^+$ T-cells have been associated with anti-tumor functions.[23-27]A review of case reports reveals a striking feature of the abscopal response in tumor types infiltrated preferentially by $CD8^+$ T-cells.[27]A pan-cancer analysis of tumors showed that renal cell carcinoma, lung adenocarcinoma, and melanoma had the highest aggregate T-cell infiltration scores.[28] Other cancer types with high aggregate T-cell infiltration scores include head and neck squamous cell carcinoma, cervical and endocervical cancer, colon and rectum adenocarcinoma, and lung squamous cell carcinoma.This suggests that an abscopal response would be more likely in one of these cancer types treated with radioimmunotherapy.

Influence of Patient Immune System

Factors that affect a patient's ability to have an abscopal response include degree of myelosuppression, neutrophil to lymphocyte ratio, and prior exposure to radiation therapy and chemotherapy.[29] The ability to have an abscopal response depends on the patient's ability to mount an immune response. Therefore, patients with decreased lymphocyte counts due to cytotoxic chemotherapy or bone marrow infiltration by tumor are less likely to have an abscopal response. Similarly, patients receiving prolonged fractionation regimens of 30 to 40 fractions are less likely to have an abscopal response due to the decreased availability of effector and memory cells.[30] T-cells are highly sensitive to radiation, with a D90 of 0.5 Gy.[31] Even with smaller, more conformal radiation therapy fields, protracted radiation therapy regimens may deliver lymphotoxic doses and exhaust T-cells, hindering their ability to produce an abscopal response.[32]

Although protracted radiation therapy regimens might reduce the incidence of an abscopal response, this does not preclude immunotherapy from being beneficial after fractionated radiation therapy. In the PACIFIC trial, patients with stage III non-small cell lung cancer who received definitive chemoradiation achieved a further response and survival benefit with durvalumab.[33] Whether the benefit of the durvalumab was enhanced by the previous chemoradiation because of an abscopal effect, or in in spite of chemoradiation's temporarily deleterious immune effects, is unknown, but certainly is an ongoing area of interest to researchers.

Influence of Overall Tumor Burden

Patients with significant tumor burden are less likely to achieve an abscopal response than patients with limited disease burden. For example, Kwon and colleagues found that patients with significant metastatic burden from prostate cancer did not benefit from CTLA-4 blockade and radiation therapy, whereas patients with limited disease burden did.[34] Similarly, Hiniker and colleagues found that patients with metastatic melanoma treated with anti-CTLA-4 and radiation therapy were more likely to achieve an abscopal response if they had a smaller volume of disease at baseline.[18] The 3 patients in their study with an abscopal response had a baseline unirradiated sum of product diameter (SPD) of 4.3 cm^2, 8.0 cm^2, and 22.8 cm^2 compared with a median value of 15.2 cm^2 in patients without an abscopal response. Other useful ways of assessing tumor burden in trials include tumor volume, tumor diameter, and number of metastatic areas.

Influence of Radiation Therapy Parameters

Radiation delivery can be altered by changes in dose, fractionation, and duration. Currently, there is no consensus on optimal radiation therapy parameters to induce an abscopal response, and pre-clinical studies have produced conflicting results. Some data suggest that single-fraction radiation is better than multiple fractions. Shen and colleagues, for instance, found that mice bearing B16 melanoma responded more favorably to 800 cGy once a week compared to 200 cGy 5 times a week.[35] However, Schaue and colleagues found that mice bearing B16 melanoma had better tumor control and immunity when treated with 2 radiation doses of 7.5 Gy compared to a single dose of 15 Gy.[36] Similarly, Dewan and colleagues found that mouse breast carcinoma cells were more likely to respond to 24 Gy in 3 fractions and 30 Gy in 5 fractions than a single fraction of 20 Gy.[37] Some studies also report similar results for both single-fraction and multiple fraction radiation.[38-40] The variability of these results may be attributed to other factors, including tumor type and radiation techniques.

Regarding the optimal sequencing of radiation therapy with immunotherapy, it is difficult to generalize. For ipilimumab, it is believed that delivering radiation therapy concurrently with immunotherapy is the best approach. Preclinical studies have shown that administering radiation therapy before

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Table 1. Ongoing Clinical Trials Examining Radiation Therapy Parameters Associated with the Abscopal Response in Patients with Metastatic Disease

Identifier*	Details	Intervention	Outcomes of Interest
NCT02710253	MD Anderson Cancer Center, metastatic cancer, phase II, n = 130	Patients randomized to receive either 50 Gy in 4 fractions using stereotactic radiation or 60-70 Gy in 10 fractions, 20-30 Gy in 5 fractions, or 30-45 Gy in 10-15 fractions using conventional external-beam radiation	Systemic disease control, treatment-related toxicities, frequency of systemic disease control
NCT02406183	Radiotherapie, metastatic melanoma, phase I, n = 13	Patients randomized to receive ipilimumab and 24 Gy in 8 fractions using stereotactic radiation or 30 Gy in 10 fractions or 36 Gy in 12 fractions using conventional external-beam radiation	Maximum tolerated dose, overall survival, progression free survival, absolute lymphocyte count, frequency of Foxp3+ Treg cells, functional analysis looking at shifts in Th1/Th2/Th17, plasmacytoid dendritic cells, myeloid-derived suppressor cells, IDO expression
NCT01896271	University of Texas Southwestern Medical Center, metastatic renal cancer, phase II, n = 26	Patients randomized to receive high dose IL-2 and stereotactic ablative RT from 8-20 Gy in 1-3 fractions	Overall survival, progression free survival, time to progression, median response duration, local control rate, tumor-specific immune response, treatment-related toxicities, health-related quality of life
NCT01862900	Providence Health and Services, metastatic breast cancer, Phase I/II, n =1 3	Patients randomized to receive anti-OX40 mAb and a single radiation dose of 15, 20, or 25 Gy to their liver or lung metastases	Maximum tolerated dose, response rate, immune response to anti-OX40 and radiation based on the number of circulating CD4+ and CD8+ T-cells
NCT02826564	Ghent University Hospital, metastatic urothelial cancer, phase I, n = 20	Patients randomized to receive stereotactic body RT prior to or concurrent with pembrolizumab therapy	Treatment-related toxicities, tumor response, immunologic response using peripheral blood samples, analyzed with FACS phenotyping, functional testing, and ELISA

* = www.clinicaltrials.gov.
Key: FACS: fluorescence-activated cell sorting, ELISA = enzyme-linked immunosorbent assay

immunotherapy results in inferior outcomes, supporting the use of concurrent delivery.[37] However, other agents such as durvalumab have been effective if administered after chemoradiation.[33] Further study is warranted regarding optimal timing of radiation therapy and immunotherapy for each type of immunotherapy agent and cancer type.

One of the few studies examining the relationship between radiation therapy parameters and the abscopal response was a retrospective review of patients with metastatic melanoma treated with radiation therapy and anti-CTLA-4.[41] The total dose, number of fractions, dose per fraction, biological equivalent dose (BED), target location, and timing of radiation therapy in relation to immunotherapy were analyzed to determine if they were associated with an abscopal response. It was found in the bivariate analysis that only a higher BED was significantly associated with an abscopal response. The target location seemed to have some effect, but the sample size for each location was not large enough for results to be significant.This potential relationship between BED and abscopal responses was supported by Marconi and colleagues, who reported in a meta-analysis that the occurrence rate of abscopal responses in pre-clinical models increased with BED.[42]

Additionally, a smaller treatment field is believed to be associated with an abscopal response. Larger treatment fields expose a larger volume of T-cells to radiation, causing them to

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Table 2. Treatment-related Toxicities for Patients Receiving Immunotherapy and Radiation Therapy

Anti-CTLA-4 and Radiation Therapy

	Comparison	Disease	N	Results
Kiess et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	15	No increase in toxicity compared to ipilimumab alone (n = 3 pruritis, n = 1 diarrhea)
Patel et al	Ipilimumab + RT vs. RT alone	Metastatic melanoma	20	Higher rate of radiation necrosis compared to RT alone (30% vs. 21%)
Qin et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	44	No increase in toxicity compared to ipilimumab alone (37 toxicities for ipilimumab vs. 33 toxicities for ipilimumab + RT)
Silk et al	Ipilimumab + RT vs. RT alone	Metastatic melanoma	5	No increase in toxicity compared to RT alone (12.5% for RT vs. 3.9% for ipilimumab + RT)
Tazi et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	10	No increase in toxicity compared to ipilimumab alone (n = 2 diarrhea)
Koller et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	70	No increase in toxicity compared to ipilimumab alone for main toxicities colitis and hypophysitis

Anti-PD-1–PD-L1 and Radiation Therapy

	Agent	Disease	N	Results
Shaverdian et al	Pembrolizumab + RT vs. pembrolizumab alone	Non-small cell lung cancer	98	Higher rate of treatment-related pulmonary toxicity compared to pembrolizumab alone (13% vs. 1%)
Ahmed et al	Nivolumab + RT vs. nivolumab alone	Metastatic melanoma	26	No increase in toxicity compared to nivolumab alone
Antonia et al	Durvalumab + chemoRT vs. chemoRT alone	Non-small cell lung cancer	475	No increase in total grade 3 toxicities compared to chemoradiation alone (29.9% vs. 26.1%)

Key: RT = radiation therapy

be exhausted and unable to mount an immune response. Proposed strategies to lower radiation-therapy-induced lymphopenia include hypofractionation, reduced treatment field size (from the elimination of elective nodal coverage or with highly conformal techniques such as stereotactic body radiation therapy or stereotactic radiosurgery), and shortening beam-on treatment times.[43]

Effect of Radiation Therapy Parameters on the Abscopal Response: Ongoing Trials

Most trials studying the combination of immunotherapy and radiation therapy are examining safety and efficacy. For the purposes of our review, we are focusing on trials studying the specific radiation therapy parameters associated with an abscopal response. We identified 5 trials examining the role of radiation dose, fractionation, and timing on the abscopal response (**Table 1**). Four of the trials are studying effects of the dose and fractionation on the abscopal response, and one is studying the effect of timing of radiation therapy in relation to immunotherapy on the abscopal response.

A trial by the MD Anderson Cancer Center (NCT02710253) is examining the response rates of patients with metastatic cancer treated with salvage radiation after progression on systemic immunotherapy. The study is recruiting any patient with at least one site of metastatic disease who has been treated with immunotherapy within the last 6 months. Patients will be treated with standard doses of 50 Gy in 4 fractions with stereotactic radiation or 60 to 70 Gy in 10 fractions, 20 to 30 Gy in 5 fractions, 20 to 30 Gy in 5 fractions, or 30 to 45 Gy in 10 to 15 fractions with conventional external-beam radiation to one or more sites of disease amenable to radiation.

A trial by Radiotherapie (NCT02406183) seeks to examine the response rates and maximum tolerated dose of patients with metastatic melanoma treated with anti-CTLA-4 and stereotactic body radiation. Patients are eligible if more than 28 days have passed since their last treatment with anti-CTLA-4 therapy and they have at least 3 extracranial metastatic lesions. Patients will be treated with doses of 24 Gy in 8 fractions, 30 Gy in 10 fractions, or 36 Gy in 12 fractions to one area of disease with concurrent anti-CTLA-4 therapy.

A trial by the University of Texas Southwestern Medical Center

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(NCT01896271) seeks to examine the response rates of patients with metastatic renal cancer treated with high-dose IL-2 and stereotactic ablative body radiation. The study is currently active for any patient with clear cell renal cell carcinoma and up to 6 sites of metastatic disease with more than one lesion > 1.5 cm. Patients will be treated with stereotactic ablative radiation, with doses varying from 8 to 20 Gy in 1 to 3 fractions followed by high-dose IL-2 treatment.

A trial by Providence Health and Services (NCT01862900) seeks to examine the response rates and maximum tolerated dose of patients with metastatic breast cancer to the liver or lung treated with stereotactic body radiation and an anti-OX40 mAb. Eligible patients have at least one lesion in either the lung or liver, with one site of disease that will not receive radiation. Patients will receive a single dose of 15 Gy, 20 Gy, or 25 Gy to the liver or lung metastasis with concurrent anti-OX40 treatment.

A trial by the Ghent University Hospital (NCT02826564) seeks to examine the response rates of patients with metastatic urothelial cancer receiving stereotactic body radiation with pembrolizumab. The study is active for patients with urothelial cancer and at least one area of metastatic disease, with one site of disease that will not receive radiation. Patients will be treated with stereotactic body radiation prior to or concurrent with systemic pembrolizumab treatment.

To gauge the immunologic response, four of the studies are using biologic correlates, which include absolute lymphocyte count, frequency of Foxp3^{+}Treg cells, shifts in Th1/Th2/Th17, number of plasmacytoid dendritic cells, number of myeloid derived suppressor cells, and IDO expression. The abscopal effect is often considered a medical spectacle without a unifying model, and its exact mechanisms have yet to be elucidated.[20] Studying these biologic correlates may shed light on the possible mechanism of the abscopal effect.

Radioimmunotherapy Toxicities

There is some concern that combining immunotherapy with radiation therapy will increase toxicities. **Table 2** summarizes the toxicity reports from 6 retrospective studies[44-49] for patients treated with ipilimumab and radiation therapy; one retrospective study[50] for patients treated with pembrolizumab and radiation therapy; one retrospective study[51] for patients treated with nivolumab and radiation therapy; and one retrospective study[33] for patients treated with durvalumab and chemoradiation. In general, for patients treated with combined immunotherapy and radiation therapy, there does not seem to be a significant increase in toxicity compared to treatment with immunotherapy alone or radiation therapy alone.

Conclusion

The combination of immunotherapy and radiation therapy is a very promising treatment regimen suggested to increase the occurrence of the previously rare abscopal response. Much uncertainty remains regarding how to best enhance the abscopal response clinically. Understanding the variables that may predict an abscopal response may help determine the necessary steps to unlock a more efficient long-term immune response after radiation therapy and convert this rare phenomenon to an everyday clinical benefit.

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