Review

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Systemic Antitumor Effects and Abscopal Responses in Melanoma Patients Receiving Radiation Therapy

Mark A. D'Andrea G. Kesava Reddy

University Cancer and Diagnostic Centers, Houston, TX, USA

Keywords
Abscopal effect · Immunostimulation · Metastatic melanoma · Radiation therapy · Systemic effects

Abstract
Background: Malignant melanoma represents the deadliest form of skin cancer with a high tendency to metastasize during the early course of the disease. Radiation therapy has long played a key role in the management of both local and metastatic melanoma. Although local radiation therapy exerts antitumor effects by damaging the cellular DNA, it also induces an important out-of-field (distant) effect known as the "abscopal effect" in nonirradiated sites. Radiation therapy-induced abscopal effects are believed to be mediated by activation and stimulation of the immune system. ***Objective:*** To provide a detailed overview of the current state of knowledge and clinical experience of radiation therapy-induced abscopal effects in patients with malignant melanoma. ***Methods:*** Using electronic databases such as MEDLINE via PubMed and Google Scholar, a systematic literature review was performed to find published clinical evidence for radiation therapy-induced abscopal effects in patients with malignant melanoma. The clinical data on radiation therapy-induced abscopal effects were reviewed and the outcomes summarized. ***Results:*** Clinical evidence of patients with malignant melanoma was gathered using databases from MEDLINE and those findings were summarized. Although the precise mechanism of the abscopal effect of radiation therapy is still not completely understood, evidence suggests that tumor cell destruction by radiation releases tumor antigens that stimulate the immune system of the host to activate the body's immune effector cells systemically and produce distant non-target antitumor effects. This forms a basis for using the radiation therapy with immunotherapy to augment the abscopal response rates. ***Conclusions:*** Current clinical evidence suggests that there is a large potential to enhance the abscopal effect when radiation therapy is combined with immunotherapeutic agents for the treatment of malignant melanoma. Ongoing and planned clinical trials may provide us with a more in-depth understanding of how this combination therapy can be optimally utilized clinically to achieve improved survival outcomes among patients with malignant melanoma.

Introduction

Malignant melanoma is an aggressive cancer with a strong tendency to metastasize during the early course of the disease. It is the fifth and sixth leading cause of all can-

G. Kesava Reddy, PhD, MHA
University Cancer and Diagnostic Centers
12811 Beamer Road
Houston, TX 77089 (USA)
kreddy_usa@yahoo.com

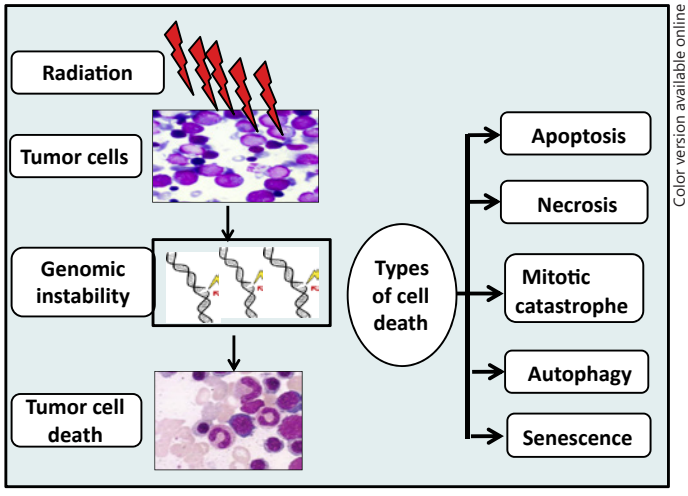

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Fig. 1. Types of tumor cell death induced by radiation therapy.

cer deaths among men and women, respectively [1, 2]. Over the past 2 decades, the incidence of melanoma has steadily increased, with more than 5% of new cases presenting with distant metastases at the time of initial diagnosis. Prior to the development of novel immunotherapeutic agents, the prognosis of metastatic malignant melanoma was dismal, with a median overall survival rate of less than 1 year and a 5-year overall survival rate under 10% [3]. However, the success of new immunotherapeutic agents such as ipilimumab, nivolumab, pembrolizumab, and other immunotherapies has heralded a new era in the effective treatment of metastatic malignant melanoma [4–8]. Despite the immunotherapeutic advances that have improved the overall survival rates, there is still a tremendous need for additional strategies to optimize the systemic treatment responses and benefits in patients with metastatic malignant melanoma.

Radiation therapy has long played a key role in the treatment of malignant metastatic melanoma, as a definitive, an adjuvant, or palliative therapy for its management. The primary mechanism of action of radiation therapy occurs through DNA damage, leading to subsequent tumor cell death. More specifically, the direct radiation effect on tumor cells results in destruction of the double-stranded DNA helix, followed by some form of tumor cell death, including apoptosis, necrosis, autophagy, mitotic catastrophe, or replicative senescence (Fig. 1). However, there is emerging evidence suggesting that radiation therapy can also stimulate the host's immune system and produce a phenomenon known as the "abscopal effect" [9–11]. In other words, local irradiation of melanoma at one site of the body induces regression of other metastatic lesions at distant, nonirradiated sites. The abscopal effect of radiation therapy was originally described by Mole in 1953 [12], in a study in which he noted that localized radiation targeted at a malignant tumor triggered systemic antitumor effects. The term *abscopal* is derived from the Latin *ab* ("position away from") and *scopus* ("target" or "mark"). Also referred to as the "distant bystander effect," this implies that radiation therapy not only has a localized action on the target tumor tissues but also has an out-of-field systemic antitumor effect [13].

Clinical evidence from melanoma and other malignancies suggests that radiation therapy can induce abscopal responses. This supports a paradigm shift from the belief that radiation functioned only as a local therapy to one that it now also elicits systemic effects [11, 14–16]. The mechanisms of how exactly radiation therapy induces the abscopal effect are not completely understood. Presumably, radiation causes a tumor cell's destruction and initiates an immune process by liberating tumor antigens, which in turn stimulate the immune system of the host to activate the immune effector cells systemically (Fig. 2). These immune effector cells then not only attack the bulk of the tumor in the irradiated area but also travel to remote metastatic sites in the body and promote tumor regression or elimination [17, 18]. Emerging evidence from preclinical and clinical studies suggests that a combination of radiotherapy and immunotherapy augments the body's antitumor response much more than either therapy alone [19–21]. Furthermore, there has been increasing clinical evidence that supports the use of a combination of targeted radiation therapy and immunotherapy. The combination therapy appears to be safe and produces improved tumor responses in patients with advanced cancers including metastatic malignant melanoma.

In this review article, we provide an overview of the current state of knowledge and clinical experience of the abscopal effect induced by radiation therapy either alone or in combination with immunotherapy for the treatment of malignant melanoma.

Methods

Study Design and Search Strategy

A systematic literature review was carried out to find published clinical evidence, primarily in peer-reviewed literature using electronic databases such as MEDLINE via PubMed and Google Scholar. Combinations of the key word "abscopal effect" with any of the following terms were used for the search in the database: radiation therapy, malignant melanoma, metastasis, systemic ef-

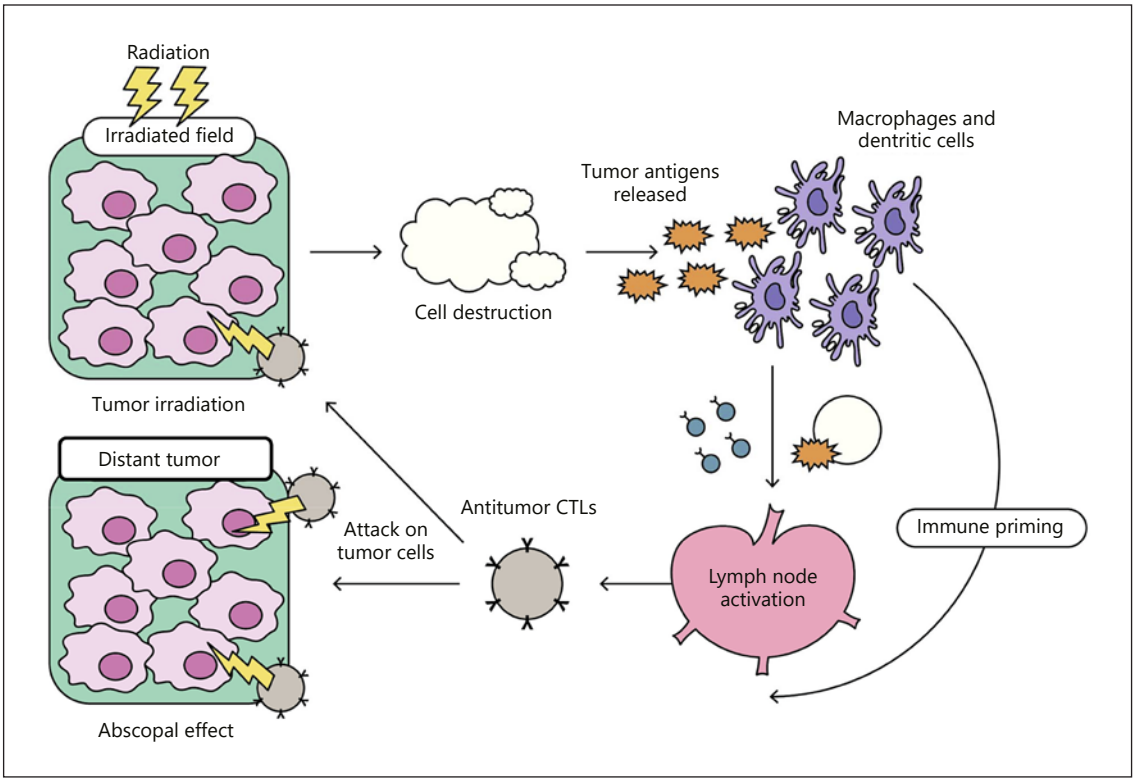

Fig. 2. Schematic drawing of the mechanism of the radiation therapy-induced abscopal effect in various malignant tumors. Localized radiation therapy of the tumor causes cell destruction and initiation of the immune process by liberating tumor antigens and producing damage-associated molecules, which lead to the maturation of dendritic cells and improved priming and activation of effector cytotoxic T lymphocytes. Tumor antigens also act as pro-inflammatory mediators, stimulating monocyte production of cytokines such as tumor necrosis factor, interleukin-1 (IL-1), IL-6, and IL-8. These cytokines, together with activated cytotoxic T lymphocytes, facilitate tumor cell elimination not only by attacking the tumor bulk in the irradiated area but also by traveling to metastatic sites and promoting tumor regression or elimination, a process known as the "abscopal effect."

fects, immunomodulation, immunostimulation, immunotherapy, and oncology. We also searched the reference lists in the publications that we obtained in an attempt to find additional relevant publications. Nonindexed journals were manually searched to find clinical evidence for radiation therapy-induced abscopal effects in patients with malignant melanoma.

Clinical Evidence of Abscopal Effects

Clinical evidence of abscopal effects in response to radiation has been reported for the past 3 decades. Notably, most of the clinical evidence of abscopal effects of radiation therapy has been reported in the form of case reports (Table 1) and small nonrandomized studies (Table 2). The clinical outcomes of these reports form a basis for the development of innovative approaches for the treatment of malignant melanoma. In early reports, the abscopal effect following radiation therapy was demonstrated in immunogenic tumors such as malignant melanoma. Innovations in immunotherapeutic strategies combining radiation therapy with targeted immune checkpoint inhibitors have revealed that the abscopal effect is more promising in malignant melanoma.

Case Studies

Recently, we reported on a 42-year-old female patient with a malignant melanoma that had metastasized to the brain experienced an abscopal effect following her central nervous system (CNS) radiation therapy [22]. The patient was initially diagnosed with a stage III melanoma on her right upper back. Initially, she underwent local surgical excision of her tumor. She remained asymptomatic for over 5 years, but later she developed a large metastatic lesion in the anterior upper right retropectoral region of her chest wall and right axilla. Based on genomic analysis,

Table 1. Summary of clinical case reports of abscopal effect of radiation therapy in malignant melanoma

Patient		Is the primary tumor treated?	Location of radiation therapy	Total radiation therapy dose, Gy	Each radiation therapy dose and fractions	Site with abscopal effect	Time to abscopal response	Study [Ref.], year
gender	age, years							
Female	42	No	Whole brain	30	2 Gy, 15 fractions	Distant chest lesions	Weeks	D'Andrea and Reddy [22], 2019
Female	65	Yes	Skin	24	8 Gy, 3 fractions	Lung lesions	Weeks	Tsui et al. [23], 2018
Female	57	No	Lung	50	10 Gy, 5 fractions	Cervical lymph node lesions	3 months	Sims-Mourtada et al. [24], 2018
Female	37	No	Whole brain	SRS: 24 WBRT: 30	SRS: not specified 3 Gy, 10 fractions	Skin lesions	After RT	Galkin et al. [25], 2018
Male	84	Yes	Skin	39	NR	Lung lesions	1 month	Komori et al. [26], 2018
Female	36	No	Brain lesions	24 for each lesion	NR	Distant nonirradiated lesions	NR	Sperduto et al. [27], 2017
Female	84	Yes	Skin	60	3 Gy, 20 fractions	Distant nonirradiated lesions	NR	Fujimura et al. [28], 2017
Female	84	Yes	Skin	60	3 Gy, 20 fractions	Distant nonirradiated lesions	NR	Fujimura et al. [28], 2017
Male	67	No	Whole brain	NR	NR	Metastatic lesions	After RT	Okwan-Duodu et al. [29], 2015
Male	44	No	CNS/brain	30	3 Gy, 10 fractions	Renal, lung, and liver lesions	3 months	Thallinger et al. [30], 2015
Male	71	Yes	Skin	30	3 Gy, 10 fractions	Lung lesions	4 months	de la Cruz et al. [31], 2014
Male	57	No	Whole brain	20	4 Gy, 5 fractions	Skin lesions	2 weeks	Teulings et al. [32], 2013
Female	ns	No	Whole brain	ns	Not specified	Pelvis and lung lesions	After RT	Kiess et al. [33], 2015
Male	67	Yes	Skin on the neck	24	8 Gy, 3 fractions	Metastatic lesions	8 months	Stamell et al. [34], 2013
Male	49	No	CNS/brain	21	7 Gy, 3 fractions	Liver and extremity lesions	After RT	Ruzevick et al. [35], 2013
Male	68	No	CNS/brain	ns	Not specified	Pelvis and spine lesions	After RT	Sullivan et al. [36], 2013
Female	33	No	Paraspinal lesion	28.5	9.5 Gy, 3 fractions	Spleen lesions	4 months	Postow et al. [37], 2012
Male	57	No	Liver lesions	54	18 Gy, 3 fractions	Liver lesions	6 months	Hiniker et al. [38], 2012
Male	28	No	Inguinal region	14.4	1.2 Gy, 12 fractions	Para-aortic lesion	9 months	Kingsley [39], 1975

CNS, central nervous system; NR, not reported; ns, not specified; SRS, stereotactic radiosurgery; RT, radiation therapy; WBRT, whole-brain radiation therapy.

Table 2. Summary of cohort study reports of abscopal effects of radiation therapy in malignant melanoma

Study type	Patients, *n*	Radiation therapy	Radiation therapy location	Total radiation therapy dose	Immunotherapy agent	Abscopal response, *n* (%)	Study [Ref.], year
Prospective	22	Palliative RT	Various lesions	Not specified	Ipilimumab	6 (27)	Sodji et al. [40], 2019
Prospective	26	HFRT	Various lesions	26 Gy, 3–5 fractions	After failure of anti-PD-1 immunotherapy	10 (38)	Saiag et al. [41], 2019
Retrospective	13	HFRT/SBRT/ SRS	Various lesions	Not specified	Pembrolizumab or nivolumab	3 (23)	Trommer et al. [42], 2019
Prospective	19	SBRT	Brain and other lesions	Not specified	Ipilimumab	4 (21)	Theurich et al. [43], 2016
Retrospective	12	RT	Various lesions	26 Gy, fractions not specified	Pembrolizumab or nivolumab	3 (25)	Ribeiro Gomes et al. [45], 2016
Prospective	18	HFRT	Various lesions	24 Gy, 4 fractions	Ipilimumab or pembrolizumab or nivolumab	6 (50)	Carvalho et al. [46], 2016
Prospective	25	SRS	Brain and other lesions	26 Gy, 4 fractions	Ipilimumab	6 (25)	Chandra et al. [44], 2015
Prospective	22	HFRT	Various lesions	Total dose not specified, 2–3 fractions	Ipilimumab	4 (18)	Twyman-Saint Victor et al. [47], 2015
Retrospective	16	WBRT/SRS	Brain lesions	36 (WBRT), 22 (SRS), fractions not specified	Ipilimumab	10 (63)	Schoenfeld et al. [48], 2015
Prospective	21	SRS	Brain, bone, and lymph node lesions	30 Gy, 10 fractions	Ipilimumab	11 (53)	Grimaldi et al. [49], 2014

HFRT, hypofractionated radiation therapy; RT, radiation therapy; SRS, stereotactic radiosurgery; SBRT, stereotactic body radiation therapy; WBRT, whole-brain radiation therapy.

she was treated with molecularly targeted agents such as dabrafenib and trametinib. However, she developed CNS symptoms due to brain metastasis prior to the initiation of the molecular targeted therapy. She was treated with dabrafenib and trametinib therapy and concurrently treated with targeted conformal radiation therapy to a dose of 30 Gy delivered in 15 fractions to her CNS lesions. Her CNS metastases improved significantly, and within 3 weeks her nonirradiated large chest mass and right axilla mass, which was outside the primary radiation treatment area, also shrank substantially, demonstrating the abscopal effect of radiation therapy.

Another recent case of the abscopal effect of radiation therapy was reported by Tsui et al. [23]. This report included a 65-year-old woman with a locally advanced mucosal melanoma of the oral cavity. The patient had a disease relapse with aggressive regional recurrence in her neck and numerous pulmonary metastases following initial treatment with surgery and adjuvant local radiation of 50 Gy in 20 fractions. Soon after the initiation of immunotherapy with pembrolizumab, the patient had a short-lived regression of the neck tumor lesion. The tumor mass in the neck had grown quickly and the lung lesions had significantly progressed. The patient underwent palliative local radiation therapy (24 Gy, 3 fractions) delivered at days 0, 7, and 21 to the neck tumor lesions with the goal to alleviate the patient's local symptoms. Remarkably, tumor regression was observed soon after the first fraction of radiation therapy. The abscopal effect of radiation therapy was observed as evidenced by regression of the patient's other, untreated lung lesions.

Sims-Mourtada et al. [24] recently reported on a case of an abscopal response in a patient with metastatic melanoma. This case involved a 57-year-old female patient who had previously received intensity-modulated radiation therapy for her metastatic melanoma to the left orbit. Later, the patient underwent surgical resection followed by postoperative radiation therapy to a dose of 37.5 Gy in

15 fractions at 2.5 Gy per fraction. In addition, she received pembrolizumab therapy with a good response. However, 1 year later she developed a single-site progression, which was evidenced by an increase in size of a right lower lobe, centrally located oligometastasis. The patient received palliative stereotactic body radiation therapy to a dose of 50 Gy in 5 fractions prescribed to the 74% isodose line, determined using a Monte Carlo dose calculation. Approximately 3 months after her radiation therapy, the patient not only had a partial response in the irradiated lesion but also developed a systemic response in the previously enlarged cervical lymph nodes, which were located outside the radiation field.

Recently, Galkin et al. [25] reported on the case of an abscopal effect induced by radiation therapy in a melanoma patient with brain metastasis. The case involved a 37-year-old woman who had initially undergone surgical resection of her malignant melanoma in the area of the sacrum. A year later, an inguinal-femoral lymphadenectomy was performed due to disease progression at that site. One year after her lymphadenectomy, magnetic resonance imaging (MRI) revealed multiple, relatively small brain metastases without edema and a mass effect. The patient underwent stereotactic radiosurgery (SRS) to the target lesions in her brain to a total radiation dose of 23 Gy. A follow-up MRI after 6 months demonstrated growth in 4 of 19 previously irradiated brain lesions and the emergence of 5 new lesions. In addition, the patient developed intradermal nodes on her arms and chest. The patient underwent a second course of SRS for all new and recurring brain lesions with marginal doses of 20 and 24 Gy. The follow-up evaluation showed dissemination of the disease along the ventricular system with the emergence of multiple small lesions, for which the patient underwent systemic treatment with cisplatin and temozolomide. In addition, she received another course of SRS with a mean dose of 20.3 Gy to a prescribed dose of 18.5 Gy. Two months after CNS radiation, the patient experienced a partial response of several irradiated lesions, and stabilization of others. However, 14 months later, she experienced disease progression, which was manifested in the emergence of new metastases. At that point of time, she received another course of SRS with a marginal dose of 24 Gy. However, she also experienced rapid development of right-sided hemiparesis and aphasia with the emergence of 10 new metastases and hemorrhage in the place of metastasis in the left parietal lobe. Later, the patient was treated with targeted systemic therapy using dabrafenib and trametinib, which led to both clinical and radiographic improvement. In addition, regression of her aphasia and hemiparesis was observed. Moreover, she had an improvement in cognitive function and diminution of her intradermal lesions over a 4-month period. Furthermore, she had partial regression of the 10 metastases that had emerged after the last radiosurgery. However, 13 months later she experienced a new recurrent disease, for which she again underwent SRS, followed by whole-brain radiation therapy (WBRT), which provided a prolonged survival of 49 months from brain metastasis detection. Overall, the patient's radiation therapy has led to the development of an abscopal effect in the form of the disappearance of her intradermal lesions without any systemic therapy.

Komori et al. [26] reported on the antitumor effects of radiation therapy combined with immunotherapy in the case of an 84-year-old man who had a metastatic melanoma on the left side of his back. Despite initial treatment with nivolumab, the patient's disease progressed and he developed metastatic lung lesions. His therapy then was changed to ipilimumab from nivolumab, as the treatment had failed to control his disease. Since a *BRAF* mutation was absent, the patient received the sequential administration of nivolumab followed by ipilimumab and radiation therapy, which was delivered to his left back for pain mitigation. The patient responded well to the treatment and the metastatic lung lesions were drastically reduced within a month. These findings suggest that when the first-line nivolumab treatment had not been effective for his metastatic melanoma, the subsequent nivolumab course with radiation therapy may have exerted something like a stimulatory booster effect on the immune system to attack the tumor.

Sperduto et al. [27] demonstrated abscopal effects of radiation therapy in the case of a 36-year-old female melanoma patient with multiple brain metastases. The patient had initially presented with a tumor mass on the right side of her neck, which was later confirmed as a malignant melanoma. She received radiation therapy (64 Gy) to the left side of her neck and scalp, followed by 3 cycles of cisplatin, interferon, and vinblastine and then interleukin-2. However, 8 months later she developed a hypermetabolic nodule in the retroperitoneum consistent with metastatic recurrence as well as brain involvement. She underwent SRS to all 3 metastatic brain lesions, after which stereotactic ablative radiotherapy was added to treat a pelvic soft tissue metastasis (25 Gy, 5 fractions over 2 weeks), followed by chemotherapy. Remarkable improvement was observed in the lesions, and the patient remained clinically and radiographically free of disease for 11 years after the diagnosis of multiple brain metasta-

ses and more than 10 years after completion of her other treatment. The authors concluded that the treatment course was consistent with the emerging literature on the abscopal effect.

Fujimura et al. [28] described 2 cases of multiple in-transit metastatic melanomas in the leg successfully treated with intensity-modulated radiotherapy (IMRT) in combination with immune checkpoint inhibitors (ipilimumab or nivolumab). In the first case, an 84-year-old Japanese woman with multiple nodules and edema on her left lower extremity had been treated for acral lentiginous melanoma and had undergone excision of some of the tumor masses and a left inguinal lymph node dissection 3 years before. Later, she was diagnosed with in-transit melanoma. Following treatment with nivolumab, she developed multiple in-transit metastases. She underwent treatment with IMRT (3 Gy, 20 fractions) in combination with ipilimumab and responded well, and the disease was under control even 6 months after the administration of the combination therapy. The second case also involved an 84-year-old Japanese woman. She had been treated for acral lentiginous melanoma and later was diagnosed with multiple in-transit melanomas. She received treatment with nivolumab, but 1 year later she had developed multiple in-transit metastases. She then underwent treatment with IMRT (3 Gy, 20 fractions) in combination with ipilimumab and responded well to the combination therapy; the disease was under control even after 3 months. Since both cases had no further development of in-transit metastasis for several months, it was suggested that the treatment with IMRT was associated with the abscopal effect when used in combination with immune checkpoint inhibitors.

In a case study by Okwan-Duodu et al. [29], it was shown that ablative radiation therapy in combination with immunotherapy was effective and produced an abscopal response in a 67-year-old male patient who presented with metastatic melanoma. The patient had an initial diagnosis of advanced metastatic melanoma with brain, subcutaneous tissue, mesenteric, pelvic, and retroperitoneal involvement. Initially, the patient was treated with SRS without any significant response. He then underwent WBRT in combination with interleukin-2 immunotherapy. He responded well to the combination therapy, suggesting that the combination of radiation therapy with immunotherapy had a synergistic effect in controlling his metastatic melanoma.

Thallinger et al. [30] reported the case of an abscopal response following treatment with radiation therapy and immunotherapy in a melanoma patient with brain metastasis. This case involved a 44-year-old male patient with melanoma metastatic to the lung, liver, kidney, and adrenal glands. A molecular analysis of the patient's melanoma biopsy showed absence of any mutations. Following 2 cycles of ipilimumab therapy, the patient developed brain metastasis. WBRT was administered by delivering a total dose of 30 Gy in 10 fractions concurrently with daily temozolomide (70 mg/m^2). In addition, the patient received an additional 2 cycles of ipilimumab therapy. The follow-up evaluation showed complete resolution of the treated brain lesions and the untreated renal lesions, along with partial regression of both the liver and the lung lesions. The complete remission of the untreated renal metastatic lesions, as well as the partial regression of both the liver and the lung metastatic lesions, is evidence for the abscopal effect of radiation therapy.

De la Cruz et al. [31] reported the case of an abscopal effect of radiation therapy in a patient with a cutaneous metastatic melanoma. This study included a 71-year-old male patient with a previously resected cutaneous melanoma who developed metastases to the lung, mediastinal lymph nodes, and subcutaneous nodules in the right temporal region. Initially, the patient declined systemic treatment for his disease. He was then offered palliative radiation therapy to a dose of 30 Gy delivered in 10 fractions for the subcutaneous nodules. At a follow-up evaluation after 4 months of cutaneous radiation therapy, the patient demonstrated complete resolution of his untreated lung lesions and significant regression of the mediastinal lymph node lesions, providing evidence for an abscopal effect of radiation therapy. The patient had no relapses in his chest or development of any new lesions in other locations for 2.5 years.

Teulings et al. [32] reported that treatment with radiation therapy produced a systemic anti-melanoma immune response in a patient with metastatic melanoma. This case study included a 67-year-old man who experienced depigmentation within the target volume several weeks after completing axillary irradiation (60 Gy, 30 fractions). Several months later, he developed brain metastases. Two weeks after completing a course of WBRT (20 Gy, 5 fractions), he developed depigmentation within and outside of the target volume, at sites not previously irradiated, suggesting an abscopal effect of radiation therapy. Disease-free survival was observed without evidence of melanoma in the patient even 3 years after the development of brain metastases. Immunologic analyses of the patient's peripheral blood, depigmented skin, and metastases demonstrated the presence of specific CD8+ T-cell and B-cell responses against melanocyte differentiation antigens.

In a retrospective analysis of the institutional melanoma database, Kiess et al. [33] reported the case of an abscopal effect in a melanoma patient with brain metastasis. In this study, a female patient was initially treated with immunotherapy using ipilimumab. However, the patient experienced continued progression of her disease in the pelvis and lungs. One year later, radiation therapy was administered to her brain lesions using SRS. A follow-up evaluation indicated that she experienced a gradual durable response in the pelvis and lungs following her brain SRS. She remained on ipilimumab therapy for 2 more years without disease recurrence. Thus, this case demonstrates that brain radiation provided not only local control of her disease in the CNS but also distant control of her metastatic lesions in the pelvis and lungs, inducing an abscopal response.

Stamell et al. [34] observed the abscopal effects of palliative radiation therapy in a patient with metastatic melanoma. Their study included a 67-year-old male who had initially presented with pigmented lesions on his head and neck, which were later diagnosed as stage IIIC malignant melanoma with multiple satellite metastases. The patient then underwent localized radiation therapy to a dose of 24 Gy delivered in 3 fractions. Eight months after his radiation therapy, all the in-transit metastases had resolved. The patient remained free of recurrent skin disease; however, after 36 months he developed nodal and brain metastases. He was treated with intracranial SRS and immunotherapy with ipilimumab. The patient remained disease free and subsequently survived for 7 more years after cutaneous radiation. Correlative immunologic analysis revealed detectable antibody titers against MAGE-A3 after the radiation therapy. The palliative radiation therapy in combination with ipilimumab had achieved a robust response in all the untreated cutaneous metastases. The long-term remission achieved with SRS plus ipilimumab for melanoma recurrence in this patient further supports the immune hypothesis of an abscopal effect of radiation therapy.

Ruzevick et al. [35] reported the interesting case of an abscopal effect in a patient with metastatic melanoma and HIV. The case involved a 48-year-old Caucasian male who underwent a highly active antiretroviral therapy for his HIV-AIDS. Two years later, the patient experienced progressive, left-sided facial, upper extremity, and lower extremity numbness, which was subsequently confirmed as metastatic melanoma upon pathological evaluation. Following surgery, the patient received immunotherapy using ipilimumab and an SRS boost to the tumor bed in the brain to a total dose of 21 Gy delivered in 3 fractions. However, he developed 2 more brain metastases: one in the right occipital lobe and another in the left frontal lobe. Both brain metastases were treated with a second course of SRS delivered to a total dose of 20 Gy in a single fraction. A restaging FDG-PET/CT scan demonstrated multiple metastases in the right and left hepatic lobes, left iliac external lymph nodes, left deep inguinal nodes, left distal thigh, left popliteal fossa, left anterior tibialis muscle, and right femur. A repeat MRI evaluation revealed an interval increase in all brain lesions, which could have been the result of post-SRS inflammation and not true progression of the underlying disease. The next 6-month follow-up showed stabilization of the patient's brain metastases, while interval PET/CT imaging showed stabilization or complete resolution of the extracranial lesions, indicating an abscopal effect due to radiation therapy.

In an interesting case report from Massachusetts General Hospital, Sullivan et al. [36] described a hypothetical interaction between a BRAF inhibitor and radiation treatment in a melanoma patient with brain metastasis. The patient was a 63-year-old man with metastatic melanoma who was positive for the *BRAF* V600E mutation. Initially, the patient had been found to have metastatic lesions in the retroperitoneum, pelvic sidewall, and right inguinal lymph nodes (largest lesion: 4 cm in size). He was enrolled in a clinical trial and treated with vemurafenib therapy. The metastatic lesions of the pelvic lymph nodes regressed after 39 weeks of vemurafenib treatment. However, his inguinal lymph nodes progressed and the disease metastasized to his brain and bones. Vemurafenib was discontinued owing to intolerance, and the patient received SRS to the single brain lesion. He then elected not to receive any further treatment. A follow-up evaluation 1 year after his radiation therapy showed not only complete resolution of his treated brain lesion but also regression of his untreated bone and inguinal lymph node lesions. A further follow-up evaluation 1.5 years after the completion of his treatment showed no evidence of disease, indicating an abscopal effect of radiation therapy.

Postow et al. [37] reported the case of an abscopal effect in a patient with metastatic melanoma who slowly progressed on ipilimumab maintenance therapy. This case involved a 33-year-old woman who had a recurrent metastatic cutaneous melanoma. She had initially undergone wide local excision of her primary lesion and biopsy of the left axillary sentinel lymph node. She remained disease free for 4 years, but later developed pulmonary metastasis. After failed treatment with chemotherapy, the patient received ipilimumab as part of a randomized open-label trial. She responded well with stable disease

while on ipilimumab therapy. She was permitted to continue with ipilimumab as maintenance therapy. After 1 year, there was slight radiographic evidence of worsening of her disease, and treatment was continued with maintenance ipilimumab, since the patient was clinically doing well. However, she developed progressive enlargement of a pleura-based paraspinal mass as well as new splenic lesions. She then underwent palliative radiation therapy (28.5 Gy, 3 fractions) for her painful paraspinal metastasis. Approximately 4 months after her radiation therapy, regression was observed in both the irradiated tumor and the nonirradiated metastases in the lung hilum and spleen. These findings suggest that radiation therapy in combination with ipilimumab was associated with an abscopal effect.

Hiniker et al. [38] reported that local radiation therapy in combination with immunotherapy achieved a complete systemic response in a patient with metastatic melanoma. This case study included a 57-year-old male patient diagnosed with stage IIA cutaneous melanoma. The patient underwent wide local excision of his primary lesion and removal of his axillary lymph nodes. He remained disease free for over 3 years, but subsequently developed a new subcutaneous nodule within the melanoma scar, which was confirmed to be recurrent melanoma. Following local excision of the satellite metastasis, the patient underwent adjuvant radiation therapy (50.4 Gy over 20 fractions) to the site of recurrence in the left posterior arm followed by adjuvant systemic therapy with high-dose interferon. The patient responded well to the treatment with no evidence of disease; however, 5 months later he developed an in-transit melanoma metastasis with liver involvement. The patient was treated with ipilimumab, but after the second dose, he was noted to have developed enlargement of 2 of his liver metastatic sites, and development of 5 new liver metastases. He underwent stereotactic ablative radiation therapy (54 Gy over 3 fractions) to the 2 metastatic sites in the liver. Six months after completing radiation therapy and ipilimumab, he was noted to have a complete response. Thus, the treatment with radiation therapy and ipilimumab therapy not only produced complete regression of his primary tumor but also achieved complete resolution of all other metastatic liver lesions, suggesting that this combination therapy supported the abscopal effects of radiation therapy.

Kingsley [39] also showed abscopal effects of radiation therapy in a patient with inguinal, pelvic, and para-aortic lymphadenopathy from melanoma. The patient was a 28-year-old male who had had a melanoma on the lateral side of the right knee for many years. Following wide excision of the melanoma, a skin graft was initially performed. A lymphangiogram of his right leg showed extensive involvement of the glands in the right inguinal region, with abnormal lymph nodes in the pelvis. The patient was treated with a full course of radiation therapy with fast neutrons delivered to a dose of 14.4 Gy in 12 fractions over 35 days to the right inguinal region. A post-treatment lymphangiogram showed remarkable regression of the lesions, and at the 9-month follow-up, the patient experienced regression of all his lymphadenopathy. He remained clinically free of disease during 1 year; however, a sudden severe rectal hemorrhage resulted in his death. A postmortem evaluation showed no evidence of residual metastatic melanoma, indicating abscopal effects of the radiation therapy.

Clinical Studies

Recently, Sodji et al. [40] reported on one of the first prospective trials evaluating the safety and efficacy of combining ipilimumab with radiation therapy in patients with metastatic melanoma. The study included 22 patients with metastatic melanoma who had received 4 cycles of ipilimumab and palliative radiation therapy to 1–2 sites of disease within 5 days of starting ipilimumab therapy. The patients were evaluated 2–4 weeks after the fourth cycle of ipilimumab therapy and every 3 months until disease progression using CT, PET, or MRI scanning. At the time of the analysis, the median follow-up was 205.5 weeks (range 78–245). At a median follow-up of 55 weeks, of the 22 patients, 3 (13.6%) had achieved a complete response and 3 (13.6%) had a partial response. Median overall survival for the cohort was 55 weeks (range 8–141), with all patients who achieved complete/partial response still alive at the time of the initial report. After a median follow-up of 205.5 weeks (range 78–245), 2 of the 3 patients with an initial complete response were still alive with no evidence of disease, and the third patient with complete response had died of an unrelated cause 78 weeks after completion of therapy. Furthermore, 2 of the 3 patients achieving partial responses eventually developed a complete response after monotherapy with pembrolizumab. The authors concluded that the combination of radiation therapy with checkpoint inhibitors had increased the rate of clinical abscopal responses in patients with a malignant melanoma.

Saiag et al. [41] recently evaluated the abscopal effects of hypofractionated radiation therapy in a cohort of advanced melanoma patients after failure of anti-programmed death-1 (PD-1) immune checkpoint inhibitor monotherapy. The study included a total of 26 advanced melanoma patients who had progressed on anti-PD-1

immune checkpoint inhibitor monotherapy. All patients received hypofractionated radiation therapy (26 Gy, 3–5 sessions). Of the 26 patients, 7 (27%) experienced a complete response, 1 had a partial response, and 3 had stable disease. An abscopal effect was seen in 10 (38%) of the 26 patients. These findings suggest that hypofractionated radiation therapy also induces abscopal responses in melanoma patients who progress on anti-PD-1 immune checkpoint inhibitor monotherapy.

A retrospective study by Trommer et al. [42] evaluated abscopal effects in patients receiving radiation therapy and pembrolizumab or nivolumab simultaneously. Of their 24 eligible patients with advanced tumors, 13 had metastatic melanoma. An abscopal effect was observed in 3 (23%) of the 13 melanoma cases who were treated with radiation therapy in combination with concurrent pembrolizumab therapy. These findings provide evidence for the clinical existence of a systemic effect of radiation plus immunotherapy, contributing to the further development of combination cancer therapy options for the management of patients with metastatic melanoma.

Theurich et al. [43] analyzed clinical data from 127 melanoma patients, including 45 patients treated with ipilimumab and radiation therapy and 82 patients treated with ipilimumab alone. The addition of radiation therapy to ipilimumab treatment significantly prolonged the median overall survival (93 vs. 42 weeks, $p = 0.0028$) of the patients. Of the 19 patients who received local peripheral radiation therapy, 4 (21%) had an abscopal response. In contrast, 3 of the 15 patients who received CNS radiation therapy without local peripheral radiation therapy had measurable abscopal effects. Importantly, the abscopal responses were mainly seen at pulmonary metastatic sites. A multivariate Cox regression analysis showed that the effect of added radiation therapy on the patients' overall survival remained statistically significant ($p = 0.05$).

Chandra et al. [44] reported on 47 consecutive metastatic melanoma patients who were treated with ipilimumab followed by radiation therapy. Their index lesion responses outside the radiation field were compared between before and after radiotherapy. The index lesions had regressed in 7 patients prior to radiation therapy, as compared with 16 cases after radiation therapy. Radiotherapy was associated with a 68% response rate in the index lesion, while two-thirds of the lesions had been progressing before radiotherapy. Radiation fractions that were ≤3 Gy were the only parameters identified to be associated with a favorable index lesion response.

Ribeiro Gomes et al. [45] evaluated abscopal effects in patients with solid metastatic tumors including metastatic melanoma. This retrospective analysis included 12 patients with progressive metastatic melanoma on anti-PD-1 immune checkpoint inhibitor therapy using nivolumab or pembrolizumab. These patients received radiation therapy while they were still on anti-PD-1 immune checkpoint inhibitor therapy. The abscopal responses seen were characterized as a response outside the irradiated field. The median time to disease progression on anti-PD-1 immune checkpoint inhibitor therapy was 3 months. Of the 12 melanoma patients, 3 experienced post-treatment abscopal responses.

Carvalho et al. [46] assessed abscopal effects of radiation therapy in combination with checkpoint inhibitors (anti-CTLA-4 and anti-PD-1) in chemotherapy-refractory patients with metastatic melanoma. The study included a total of 18 patients with progressive metastatic melanoma previously treated with at least 2 lines of chemotherapy who received palliative radiation therapy to 1 metastatic site during CTLA-4 or anti-PD-1 immune checkpoint inhibitor therapy. Of the 18 patients, 12 received nivolumab, 3 received pembrolizumab, and the remaining 3 received ipilimumab. A majority of the patients received radiation therapy at a dose of 24 Gy delivered in 3 fractions. The metastatic sites irradiated included the brain, stomach, liver, lymph nodes, breast, bone, soft tissue, and lung. After a median follow-up of 6 months, 12 patients experienced a response in their nonirradiated metastatic sites, characterizing an abscopal effect of radiation therapy. In addition, another 8 patients achieved a significant improvement in local disease control in the irradiated area despite the lack of a systemic response. These findings suggest that radiation therapy in combination with CTLA-4 or anti-PD-1 immune checkpoint inhibitor therapy produced a significant rate of abscopal effects and improvement in local disease control in patients with metastatic melanoma.

A phase I study evaluated the clinical effectiveness of hypofractionated radiation therapy combined with ipilimumab in melanoma patients with multiple metastases [47]. The trial included a total of 22 patients with multiple melanoma metastases. A single index lesion was irradiated with hypofractionated radiation, delivered over 2 or 3 fractions, followed by 4 cycles of anti-CTLA-4 ipilimumab therapy. The findings of the study indicate that the combination therapy resulted in excellent local control (with 1 complete response, 6 partial responses, and 9 patients with stable disease) at the site of radiation. An evaluation of the nonirradiated lesions by computed tomography imaging revealed that 4 of the 22 patients (18%)

Table 3. Current and ongoing clinical trials assessing abscopal effects of radiation therapy in combination with immunotherapy in melanoma

ClinicalTrials.gov identifier	Study phase	Radiation therapy	Total radiation therapy dose and fractions	Immunotherapy agent	Endpoint	Location
NCT03354962	Phase I/II	SBRT	Recommended optimal dose	Nivolumab plus ipilimumab	Abscopal effect is defined as tumor shrinkage ≥20% compared to baseline in the control lesion (nonirradiated and distant lesion) at the end of the 6-week period of treatment without evidence of clinical progression	France
NCT02562625	Phase II	RT	24 Gy (8 Gy in 3 fractions)	Pembrolizumab	To assess the abscopal response to RT with pembrolizumab	UK
NCT01689974	Phase II	IMRT/ IGRT	30 Gy (6 Gy in 5 fractions)	Ipilimumab	To assess the abscopal effect of RT with ipilimumab	USA
NCT01416831	Phase II	SBRT	20 or 40 Gy (20 Gy in 1 or 20 Gy in 2 fractions)	Interleukin-2	To assess the efficacy of RT combined with high-dose interleukin-2	USA
NCT01973608	Phase II	SBRT	24 Gy (8 Gy in 3 fractions)	MSB0010445 (targeted modified interleukin-2)	To assess the abscopal response of RT with MSB0010445	USA
NCT02115139	Phase II	WBRT	30 Gy (10 Gy in 3 fractions)	Ipilimumab	To assess an immune-related response to the therapy	Spain
NCT03850691	Phase II	WBRT	Dose not specified	Interleukin-2 or nivolumab or ipilimumab	To assess the safety and efficacy (objective response rate) of RT	USA
NCT03693014	Phase II	SBRT	Variable doses	Progressed on ipilimumab, nivolumab, pembrolizumab, or atezolizumab	To assess the efficacy and safety of several doses of RT	USA
NCT02523313	Phase II	RT	Variable doses	Nivolumab or nivolumab plus ipilimumab	To assess the safety and efficacy of immunotherapy with nivolumab or nivolumab plus ipilimumab versus a double-placebo control as a post-radiation treatment for stage IV melanoma with no evidence of disease	Germany
NCT02097732	Phase II	SRS	Dose not specified	Ipilimumab	To evaluate the efficacy of using standard immune therapy for melanoma prior to SRS (ipilimumab induction)	USA
NCT02406183	Phase I	SBRT	24, 30, 36 Gy (3 Gy in 8 fractions) (3 Gy in 10 fractions) (3 Gy in 12 fractions)	Ipilimumab	To assess the safety and tolerability of ipilimumab in combination with high-dose RT	Belgium
NCT01703507	Phase I	WBRT	Variable	Ipilimumab	To assess the safety of RT combined with ipilimumab	USA
NCT02659540	Phase I	RT	27 Gy (9 Gy in 3 fractions)	Nivolumab plus ipilimumab	To assess the safety and tolerability of ipilimumab and nivolumab in combination with RT	USA

IMRT, intensity-modulated radiation therapy; IGRT, image-guided radiation therapy; RT, radiation therapy; SRS, stereotactic radiosurgery; SBRT, stereotactic body radiation therapy; WBRT, whole-brain radiation therapy.

had a partial response and another 4 had stable disease. The median progression-free survival and overall survival was 3.8 and 10.7 months, with a median follow-up of 18.4 and 21.3 months (18.0 and 21.3 for patients without an event), respectively. Thus, the antitumor responses of the nonirradiated lesion sites indicate a post-treatment abscopal effect of the combined modalities of radiation and immunotherapy.

Schoenfeld et al. [48] analyzed 16 melanoma patients who received SRS to their brain metastases plus ipilimumab therapy and systematically evaluated their abscopal responses by following the largest extracranial lesion. The index lesions were reduced in size after the brain-directed radiation therapy in 63% of those patients who received both radiation therapy and ipilimumab within 3 months of therapy. The median overall survival was longer (17 months) among patients who had initially been treated with SRS than among all patients (14 months).

Grimaldi et al. [49] analyzed the abscopal effects of radiation therapy in 21 patients with advanced melanoma that was progressing even after treatment with ipilimumab. Of these 21 patients, 13 (62%) received radiation therapy to the brain, 4 to the bone, 2 to distant lymph nodes, and 2 to cutaneous metastases. Within a median follow-up of 1 month, abscopal responses were seen in 11 patients (53%), 9 of whom had partial responses and 2 had stable disease. The median overall survival among all 21 patients was 13 months. The median overall survival was longer among those patients who experienced an abscopal response (22.4 vs. 8.3 months, $p = 0.02$). Abscopal responses were only observed in patients exhibiting local responses to radiation therapy.

Current Clinical Trials of Radiation in Combination with Immunotherapy

Promising clinical and preclinical data from combined approaches with radiation therapy and immunotherapy have led to a number of phase I–II clinical trials in patients with advanced melanoma and other cancers. Recently, the number of clinical trials assessing the clinical effectiveness of radiation therapy in combination with immunotherapy has been increasing rapidly (Table 3). These clinical trials are initial explorations and represent the beginning of a new era of assessing abscopal effects in an oncologic setting. Importantly, these studies often evaluate the effects of radiation therapy in combination with immunotherapy in metastatic disease, and at a stage where radiation therapy is traditionally reserved for local palliation of symptoms.

Conclusion and Future Perspectives

Together, the findings of the published studies suggest that radiation therapy-induced abscopal responses have awakened clinical scientists to rethink the critical role of radiation in the treatment of advanced malignant tumors including metastatic melanoma. Abscopal effects following radiation therapy appear to be mediated by a number of different mechanisms involved in the tumor's microenvironment. In addition, there is a large body of evidence that suggests there is a potential to enhance the abscopal effects when radiation therapy is combined with immunotherapeutic agents for the treatment of malignant melanoma. Despite the evidence that radiation therapy can cause liberation of tumor antigens, which then activate the immune system and enhance systemic immune responses, the optimal partnering with immunotherapeutic agents to maximize the clinical effectiveness of this treatment remains to be explored in other malignant tumor types. Ongoing and planned clinical trials in support of this combination therapy can address those limitations and may provide a better understanding of how to optimize the clinical benefits of radiation therapy used in combination with novel immunotherapies for the treatment of malignant melanomas.

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M.A.D. participated in the study design; critically reviewed the data and revised the manuscript; gave final approval; and agrees to be accountable for all aspects of the work ensuring its integrity and accuracy. G.K.R. contributed to the study's conception and design; collected, analyzed, and interpreted the data; drafted and critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of the work ensuring its integrity and accuracy.

References

1 Tripp MK, Watson M, Balk SJ, Swetter SM, Gershenwald JE. State of the science on prevention and screening to reduce melanoma incidence and mortality: the time is now. CA Cancer J Clin. 2016;66(6):460–80.
2 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62(1):10–29.
3 Miller AJ, Mihm MC Jr. Melanoma. N Engl J Med. 2006;355(1):51–65.
4 Eggermont AM, Robert C. New drugs in melanoma: it's a whole new world. Eur J Cancer. 2011;47(14):2150–7.
5 Beaver JA, Theoret MR, Mushti S, He K, Libeg M, Goldberg K, et al. FDA approval of nivolumab for the first-line treatment of patients with $BRAF^{V600}$ wild-type unresectable or metastatic melanoma. Clin Cancer Res. 2017;23(14):3479–83.
6 Hazarika M, Chuk MK, Theoret MR, Mushti S, He K, Weis SL, et al. U.S. FDA approval summary: nivolumab for treatment of unresectable or metastatic melanoma following progression on ipilimumab. Clin Cancer Res. 2017;23(14):3484–8.
7 Barone A, Hazarika M, Theoret MR, Mishra-Kalyani P, Chen H, He K, et al. FDA approval summary: pembrolizumab for the treatment of patients with unresectable or metastatic melanoma. Clin Cancer Res. 2017;23(19):5661–5.
8 Chuk MK, Chang JT, Theoret MR, Sampene E, He K, Weis SL, et al. FDA approval summary: accelerated approval of pembrolizumab for second-line treatment of metastatic melanoma. Clin Cancer Res. 2017;23(19):5666–70.
9 D'Andrea MA, Reddy GK. Systemic immunostimulatory effects of radiation therapy improves the outcomes of patients with advanced NSCLC receiving immunotherapy. Am J Clin Oncol. 2019 [Epub ahead of print].
10 D'Andrea MA, Reddy GK. Extracranial abscopal effects induced by brain radiation in advanced lung cancer. Am J Clin Oncol. 2019;42(12):951–7.
11 D'Andrea MA, Reddy GK. The systemic immunostimulatory effects of radiation therapy producing overall tumor control through the abscopal effect. J Radiat Oncol. 2019;8:143–56.
12 Mole RH. Whole body irradiation; radiobiology or medicine? Br J Radiol. 1953;26(305):234–41.
13 Kaminski JM, Shinohara E, Summers JB, Niermann KJ, Morimoto A, Brousal J. The controversial abscopal effect. Cancer Treat Rev. 2005;31(3):159–72.
14 Siva S, MacManus MP, Martin RF, Martin OA. Abscopal effects of radiation therapy: a clinical review for the radiobiologist. Cancer Lett. 2015;356(1):82–90.
15 Brix N, Tiefenthaller A, Anders H, Belka C, Lauber K. Abscopal, immunological effects of radiotherapy: narrowing the gap between clinical and preclinical experiences. Immunol Rev. 2017;280(1):249–79.
16 Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer. 2016;40(1):25–37.
17 Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. Curr Probl Cancer. 2016;40(1):10–24.
18 Hlavata Z, Solinas C, De Silva P, Porcu M, Saba L, Willard-Gallo K, et al. The abscopal effect in the era of cancer immunotherapy: a spontaneous synergism boosting anti-tumor immunity? Target Oncol. 2018;13(2):113–23.
19 Ko EC, Formenti SC. Radiotherapy and checkpoint inhibitors: a winning new combination? Ther Adv Med Oncol. 2018;10:1758835918768240.
20 Shevtsov M, Sato H, Multhoff G, Shibata A. Novel approaches to improve the efficacy of immuno-radiotherapy. Front Oncol. 2019;9:156.
21 Meng X, Feng R, Yang L, Xing L, Yu J. The role of radiation oncology in immuno-oncology. Oncologist. 2019;24(Suppl 1):S42–S52.
22 D'Andrea MA, Reddy GK. Extracranial systemic antitumor response through the abscopal effect induced by brain radiation in a patient with metastatic melanoma. Radiat Oncol J. 2019;37(4):302–8.
23 Tsui JM, Mihalcioiu C, Cury FL. Abscopal effect in a stage IV melanoma patient who progressed on pembrolizumab. Cureus. 2018;10(2):e2238.
24 Sims-Mourtada J, Casteneda S, Huang D, McGlade J, Shah S, et al. Dosimetric characterization of an abscopal response in a patient with oligometastatic melanoma undergoing concurrent treatment with pembrolizumab and stereotactic body radiotherapy (SBRT). Cancer Stud Mol Med. 2018;4:1–4.
25 Galkin MV, Golanov AV, Vetlova E, Banov S, Kostjuchenko VV. Advanced survival in patients with multiple irradiations for brain melanoma metastases and associated abscopal effect. Cureus. 2018;10(1):e2034.
26 Komori T, Otsuka A, Irie H, Horiguchi A, Honda T, Kabashima K. Drastic effect on giant lung metastatic melanoma by sequential administration of nivolumab with ipilimumab/radiation combination therapy. J Dermatol. 2018;45(1):e7–e8.
27 Sperduto W, King DM, Watanabe Y, Lou E, Sperduto PW. Case report of extended survival and quality of life in a melanoma patient with multiple brain metastases and review of literature. Cureus. 2017;9(12):e1947.
28 Fujimura T, Kambayashi Y, Furudate S, Hidaka T, Sato Y, Tanita K, et al. Successful treatment of multiple in-transit melanomas on the leg with intensity-modulated radiotherapy and immune checkpoint inhibitors: report of two cases. J Dermatol. 2017;44(5):592–5.
29 Okwan-Duodu D, Pollack BP, Lawson D, Khan MK. Role of radiation therapy as immune activator in the era of modern immunotherapy for metastatic malignant melanoma. Am J Clin Oncol. 2015;38(1):119–25.
30 Thallinger C, Prager G, Ringl H, Zielinski C. Abscopal effect in the treatment of malignant melanoma [in German]. Hautarzt. 2015;66(7):545–8.
31 de la Cruz V, Sanz Á, Torrego JC, Fiorini AB. The strange abscopal effect [in Spanish]. Rev Clin Esp (Barc). 2014;214(3):170–1.
32 Teulings HE, Tjin EP, Willemsen KJ, Krebbers G, van Noesel CJ, Kemp EH, et al. Radiation-induced melanoma-associated leucoderma, systemic antimelanoma immunity and disease-free survival in a patient with advanced-stage melanoma: a case report and immunological analysis. Br J Dermatol. 2013;168(4):733–8.
33 Kiess AP, Wolchok JD, Barker CA, Postow MA, Tabar V, Huse JT, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. Int J Radiat Oncol Biol Phys. 2015;92(2):368–75.
34 Stamell EF, Wolchok JD, Gnjatic S, Lee NY, Brownell I. The abscopal effect associated with a systemic anti-melanoma immune response. Int J Radiat Oncol Biol Phys. 2013;85(2):293–5.
35 Ruzevick J, Nicholas S, Redmond K, Kleinberg L, Lipson EJ, Lim M. A patient with HIV treated with ipilimumab and stereotactic radiosurgery for melanoma metastases to the brain. Case Rep Oncol Med. 2013;2013:946392.
36 Sullivan RJ, Lawrence DP, Wargo JA, Oh KS, Gonzalez RG, Piris A. Case records of the Massachusetts General Hospital. Case 21-2013. A 68-year-old man with metastatic melanoma. N Engl J Med. 2013;369(2):173–83.
37 Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med. 2012;366(10):925–31.
38 Hiniker SM, Chen DS, Reddy S, Chang DT, Jones JC, Mollick JA, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. Transl Oncol. 2012;5(6):404–7.
39 Kingsley DP. An interesting case of possible abscopal effect in malignant melanoma. Br J Radiol. 1975;48(574):863–6.

40 Sodji Q, Gutkin PM, Hiniker SM, Swetter S, Reddy S, Knox SJ. Durability of abscopal effect in metastatic melanoma patients after the combination of radiation therapy and ipilimumab: update on a prospective clinical trial. Int J Radiat Oncol Biol Phys. 2019;105(1):S61–S62.
41 Saiag P, Baghad B, Fort M, Aouidadd I, Roger A, Mazeron JJ, et al. Efficacy of hypofractionated radiotherapy (Rx) in melanoma patients who failed anti-PD-1 monotherapy: assessing the abscopal effect. J Clin Oncol. 2019;37(15_Suppl):9537.
42 Trommer M, Yeo SY, Persigehl T, Bunck A, Grüll H, Schlaak M, et al. Abscopal effects in radio-immunotherapy-response analysis of metastatic cancer patients with progressive disease under anti-PD-1 immune checkpoint inhibition. Front Pharmacol. 2019;10:511.
43 Theurich S, Rothschild SI, Hoffmann M, Fabri M, Sommer A, Garcia-Marquez M, et al. Local tumor treatment in combination with systemic ipilimumab immunotherapy prolongs overall survival in patients with advanced malignant melanoma. Cancer Immunol Res. 2016;4(9):744–54.
44 Chandra RA, Wilhite TJ, Balboni TA, Alexander BM, Spektor A, Ott PA, et al. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. Oncoimmunology. 2015;4(11):e1046028.
45 Ribeiro Gomes J, Schmerling RA, Haddad CK, Racy DJ, Ferrigno R, Gil E, et al. Analysis of the abscopal effect with anti-PD1 therapy in patients with metastatic solid tumors. J Immunother. 2016;39(9):367–72.
46 Carvalho RF, Ferrigno R, Marotta RC, Amarantes MPF, Schmerling RA, Haddad CK, et al. Abscopal effect in patients with metastatic melanoma treated with checkpoint inhibitors (anti-CTLA-4 and anti-PD1): a retrospective analysis of a single institution. Int J Radiat Oncol Biol Phys. 2016;96(2 Suppl):S159.
47 Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520(7547):373–7.
48 Schoenfeld JD, Mahadevan A, Floyd SR, Dyer MA, Catalano PJ, Alexander BM, et al. Ipilimumab and cranial radiation in metastatic melanoma patients: a case series and review. J Immunother Cancer. 2015;3:50.
49 Grimaldi AM, Simeone E, Giannarelli D, Muto P, Falivene S, Borzillo V, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. Oncoimmunology. 2014;3:e28780.