# Brain Radiation Induced Extracranial Abscopal Effects in Metastatic Melanoma

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**Abstract:** Historically, the brain has been viewed as a specialized neurovascular inert organ with a distinctive immune privilege. Therefore, radiation-induced extracranial abscopal effects would be considered an unusual phenomenon due to the difficulty of the immunogenic signaling molecules to travel across the blood-brain barrier (BBB). However, it is now possible that localized central nervous system radiation has the ability to disrupt the structural integrity of the BBB and increase its endothelial permeability allowing the free passage of immunogenic responses between the intracranial and extracranial compartments. Thus, the nascent tumor–associated antigens produced by localized brain radiation can travel across the BBB into the rest of the body to modulate the immune system and induce extracranial abscopal effects. In clinical practice, localized brain radiation therapy–induced extracranial abscopal effects are a rarely seen phenomenon in metastatic melanoma and other advanced cancers. In this article, we provide a detailed overview of the current state of knowledge and clinical experience of central nervous system radiation–induced extracranial abscopal effects in patients with malignant melanoma. Emerging data from a small number of case reports and cohort studies of various malignancies has significantly altered our earlier understanding of this process by revealing that the brain is neither isolated nor passive in its interactions with the body's immune system. In addition, these studies provide clinical evidence that the brain is capable of interacting actively with the extracranial peripheral immune system. Thus, localized radiation treatment to 1 or more locations of brain metastases can induce extracranial abscopal responses. Collectively, these findings clearly demonstrate that localized brain radiation therapy–induced abscopal effects traverses the BBB and trigger tumor regression in the nonirradiated extracranial locations.

**Key Words:** abscopal effect, brain metastasis, central nervous system lesions, immunostimulation, molecular targeted therapy, radiation therapy, skin cancer, tumor regression

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Over the years, radiation has been used as an effective local treatment modality to treat various malignant diseases. It plays a crucial role in the treatment of metastatic tumors including melanoma.[1–3] Recent estimates suggest that ~60% of all cancer patients receive radiation therapy at some point during the course of their disease.[4–6] Radiation therapy is indicated for both definitive treatment of localized tumors as well as for palliation of symptoms from widely metastatic disease. Traditionally, radiation therapy is administered by delivering radiation in multiple small daily doses, over several weeks to control the local tumor growth while minimizing the injury risk to the healthy tissue adjacent to the tumor. However, advances in radiation technologies have allowed better planning and precise delivery of radiation to targeted tumors while limiting the exposure of healthy tissues to radiation. Moreover, the advent of sophisticated imaging technologies such as computed tomography and magnetic resonance imaging (MRI) together with innovative radiation treatment devices has led to the development of 3-dimensional conformal radiation therapy, which utilizes 3-dimensional based beams to deliver higher doses of radiation to the tumor.[7,8] Other innovative techniques such as image-guided radiation therapy, intensity-modulated radiation therapy stereotactic radiosurgery (SRS) and stereotactic body radiation therapy have transformed the precision and delivery of radiation to the tumor target sites and broadened its range of clinical applications leading to an improved understanding of the radiobiology of radiation therapy.

## DNA DAMAGING AND CYTOTOXIC EFFECT OF RADIATION

Focused ionizing radiation is a powerful cytotoxic tool that can be used to specifically kill tumor cells and shrink tumors at target sites.[9,10] The DNA molecule is the main target of radiation within tumor cells. The so-called lethal effect of radiation is mainly attributed to the destruction of double standard DNA molecules that leads to cellular damage.[11] Consequently, radiation treatment effectively arrests tumor growth and causes cell death leading to tumor regression and local tumor elimination.[10,12,13] During the process of tumor cell destruction, the direct radiation effect occurs to the targeted tumor cells in the pathway of the radiation beam (Fig. 1). The DNA damage and subsequent tumor cell death caused by the ionizing radiation has been ascribed to 5 basic principles known as the 5 "R's" of radiation biology.[14] These include repair, repopulation, redistribution, reoxygenation, and radiosensitivity, which are critical to achieve the therapeutic goal of tumor eradication in radiation therapy.

## ABSCOPAL EFFECTS OF RADIATION THERAPY

The traditional view of radiation-induced tumor cell death was limited in the context of the host antitumor immunity and tumor microenvironment. With a new understanding of radiation biology, a newly defined form of tumor cell death can occur through the immunostimulatory effects of radiation therapy that activates the local immune system and ultimately alters the tumor microenvironment.[15,16] Consequently, the altered tumor microenvironment can prompt a reactivation of the immune response, a phenomenon called an "abscopal effect" (*ab scopus*, away from the target) of radiation therapy.[15] In 1953, the British radiologist Mole[17] introduced the term "abscopal effect" to describe systemic antitumor responses triggered by localized radiation at distance nonirradiated sites. Although the phenomenon of the abscopal effect was described over 5 decades ago, it only recently gained importance in

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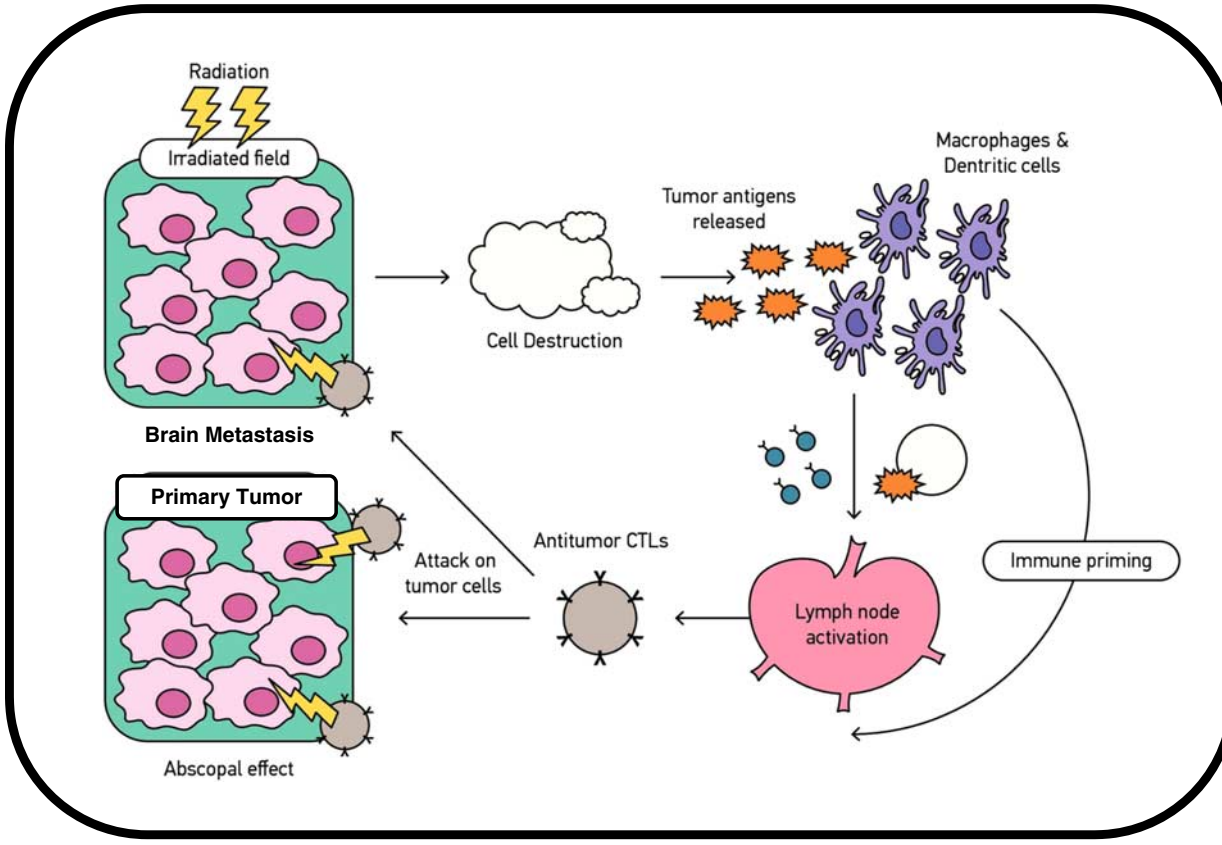


**FIGURE 1.** Schematic drawing of the mechanism of the localized brain radiation therapy–induced extracranial abscopal effect in metastatic melanoma. Localized brain radiation of the metastatic lesion causes tumor cell destruction and initiation of the immune process by liberating tumor antigens and producing damage-associated molecules, which lead to the maturation of dendritic cells and improved priming and activation of effector cytotoxic T lymphocytes (CTLs). Tumor antigens also act as proinflammatory mediators, stimulating monocyte production of the cytokines tumor necrosis factor, interleukin-1 (IL-1), IL-6, and IL-8. These cytokines together with the activated CTLs facilitate tumor cell elimination by attacking not only the tumor bulk in the irradiated area but also travel to nonirradiated locations and promote tumor regression or elimination, a process known as an abscopal effect. full color online

cancer treatment mainly in the form of case reports.[15,18] There is now a growing interest in the abscopal effects of radiation therapy because of the increasing use of this modality in conjunction with gene-targeted and immunotherapy in patients with various types of malignant tumors.

## PRECLINICAL EVIDENCE OF ABSCOPAL EFFECT

Despite the abscopal effect of radiation therapy was described in 1953, its clinical experience has been largely limited to only sporadic case reports for most of the last 5 decades. However, the knowledge about radiation therapy–induced antitumor systemic immune mechanisms and the resulting abscopal effects is largely based on preclinical experience. The findings from these preclinical studies provide some of the molecular mechanisms that are involved in the induction of systemic antitumor responses by local radiation therapy. Zhang and Niedermann[19] reported that in mice bearing 2 B16-CD133 melanoma tumors treated with radiation therapy (3×9.18 Gy in 3 or 5 d or with 5×6.43 Gy in 10 d) and anti-programmed cell death protein 1 antibody therapy–induced T lymphocytes or T cells infiltrate the irradiated tumor can provoke local and systemic antitumor effects. The combination treatment not only inhibited the growth of the irradiated primary tumor but also produced regression in the nonirradiated secondary tumor sites indicating the abscopal effect of radiation therapy. Using a metastatic murine lung cancer model, Chakravarty et al[20] reported that the primary tumor treated with high-dose local radiation therapy (60 Gy) and Fms-related tyrosine kinase 3 ligand has resulted in spontaneous regression of several metastatic lesions indicating radiation therapy–induced abscopal effect. Demaria et al[21] demonstrated that the systemic outcome is mediated by the immune system and that T cells are required for distant tumor regression after combined local radiation and Fms-related tyrosine kinase 3 ligand treatment in a mouse model of mammary carcinoma.

Mice with melanoma tumors treated with radiation therapy using 25 Gy in 1 fraction had fewer lung metastatic lesions than mice that received no radiation therapy.[22] In addition, mice that had previously received an ex vivo irradiated melanoma vaccine had greater tumor infiltration by $CD8^+$ T cells suggesting dendritic cell (DC)-mediated phagocytosis to reduce metastatic lesions following radiation therapy. Similarly, Lee et al[23] reported that the efficacy of high-dose ablative radiotherapy in a mouse model of melanoma was mediated by $CD8^+$ T cells. Several other studies also have found that systemic antitumor immune effects of either radiation therapy alone or in combination with immunotherapy were dependent on $CD8^+$ T cells.[24–27] Interestingly, Takeshima et al[28] have shown that local radiation therapy treatment of EG7 tumors in one leg of

the mouse combined with Th1 cell therapy arrests tumor growth in both legs. These findings further prove the abscopal effects of radiation therapy when combined with supplemental immune stimulation/immune therapy.

The demonstration in various preclinical models that radiation therapy induces antitumor $CD8^+$ T cells when applied to an in vivo growing tumor has fostered enthusiasm for its use as a tool to convert a tumor into an in situ vaccine for patients with different malignant tumors including melanoma. Although T cell contribution to regression of the irradiated tumor was well proven decades ago, the concept of the understanding how radiation therapy–induced T cell responses that are effective against nonirradiated distant metastases has emerged only recently. Nonetheless, the immune system plays an integral role in the induction of abscopal effects and systemic antitumor response after radiation therapy.

## IMMUNOLOGIC BASIS OF ABSCOPAL EFFECT

Currently, the molecular basis of radiation therapy–induced abscopal effects has not been precisely established. However, existing evidence indicates that immune-mediated cell death plays a prominent role in radiation-induced abscopal effect (Fig. 2).[29] The abscopal effects of radiation are believed to be mediated by tumor antigen primed T lymphocytes (T cells) which are released from the tumor following exposure to local radiation.[29,30] After the liberation of the tumor antigens from the destroyed tumor cells by local radiation therapy, the primed T cells travel to metastatic tumor sites, activate the immune system, and promote tumor regression. Thus, the localized radiation-induced tumor cell death leads to the release of various immunogenic signaling molecules that subsequently trigger the release of a number of endogenous damage-associated molecular patterns.[31] The endogenous damage-associated molecular pattern signaling molecules such as calreticulin, a high-mobility group box 1 protein, ATP, and others trigger DCs and contribute to the priming of the body's immune system through the improved antigen presentation to T cells. During the process of radiation therapy–induced immunomodulation, the release of tumor antigens acts as proinflammatory mediators, stimulating monocyte production of the cytokines such as tumor necrosis factor, interleukin-1 (IL-1), IL-6, IL-8, and other signaling molecules.[15,30] Consequently, alterations occur in the tumor microenvironment leading to an influx of immune cells to the lesion sites through antigen-presenting cells that specifically recognize tumor-specific antigens released by the dead cells. Collectively, these events promote tumor cell elimination by primed T cells. However, to induce an abscopal effect by radiation a sufficient volume of the T cells are required. In addition, adequate production and presentation of tumor-associated antigen by antigen-presenting cell to T cells is necessary to produce specific killer T cells for the tumor cells at primary and metastatic locations.[32]

Although the changes in the tumor microenvironment caused by radiation are not precisely established, evidence suggests that the immune system senses those alterations and triggers immune response pathways resulting in several areas of systemic stimulation.[33] Studies have shown that radiation therapy can produce epitope spreading, thereby increasing the diversity of the T-cell receptor repertoire of intratumoral T cells and broadening the antitumor response.[34] Moreover, the intratumoral T cells are known to induce and improve an immune response specific to the tumor cell.[35] Therefore, an improved understanding of radiation therapy–induced abscopal effects

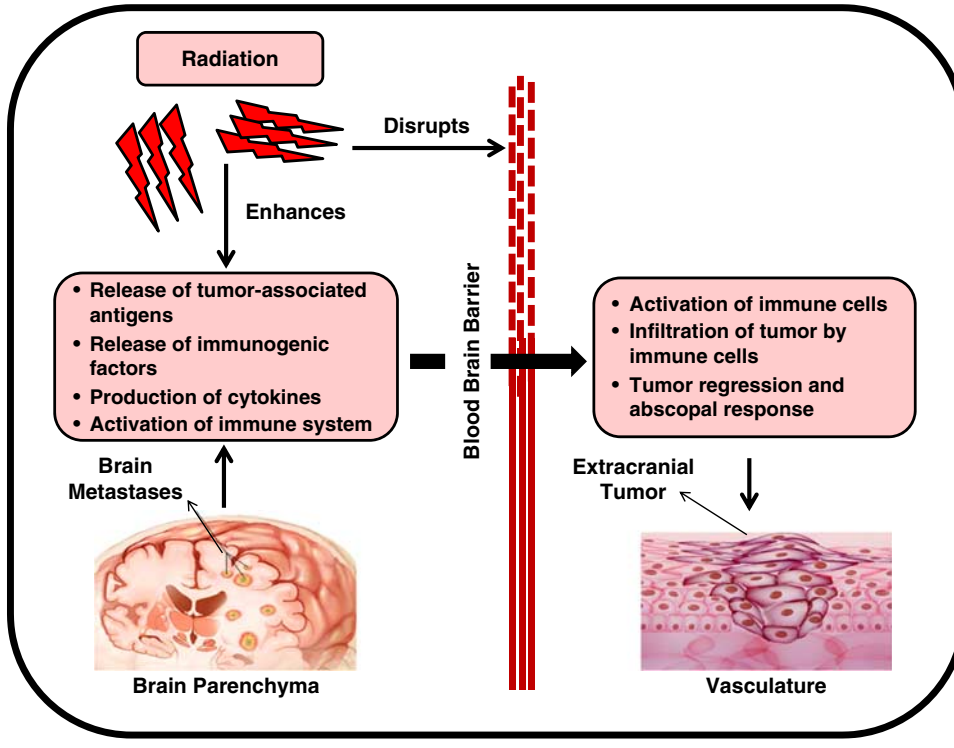


**FIGURE 2.** Schematic representation depicting the potential interactions between radiation, the blood-brain barrier, and antitumor immunity. Localized brain radiation therapy disrupts the structural integrity of the blood-brain barrier and increases its permeability allowing the passage of immunogenic signaling molecules from intracranial to extracranial compartments resulting in an abscopal response. full color online



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and its immunologic correlates has clinical implications in combining radiation therapy with immunotherapy to boost abscopal response rates. There is now a growing consensus for combining radiation therapy with immunotherapy for the treatment of brain metastases, particularly in those patients who have metastatic melanoma.

## MALIGNANT MELANOMA AND BRAIN METASTASES

Malignant melanoma is a neoplasm of melanocytes that usually occurs in the skin. Being a devastating disease, malignant melanoma is considered as the deadliest form of skin cancer. It is the sixth most common cancer in the United States with an estimated incidence of 96,480 new cases and 7230 disease-related deaths in 2019.[36] Malignant melanoma has a high tendency to metastasize during the early course of the disease. Brain metastasis is the most frequent finding in patients with advanced melanoma.[37] Approximately 20% of melanoma patients have brain metastasis at the time of their diagnosis, and over 50% develop brain metastasis during the course of their disease.[38–40] Historically, melanoma patients with brain metastasis have been considered to have an extremely poor prognosis. Death is an inevitable outcome in the majority of patients due to rapid disease progression in the brain. The median overall survival of the patients with brain metastasis is dismal, ranging only 17 to 22 weeks.[38,41] In fact, until relatively recently, treatment approaches for melanoma patients with brain metastasis had been extremely limited. However, an ever-expanding understanding of the underlying molecular mechanisms of tumor development have led to the use of novel treatment strategies aimed at eradicating various malignant metastatic cancers including melanoma.

The recent 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.[42–46] Although the novel immunotherapeutic agents have improved the overall survival rates, there is still a tremendous need for additional strategies to optimize treatment responses and benefits in melanoma patients with brain metastasis. The improvements in imaging technology, delivery of focused radiation therapy, development of novel targeted therapies, innovations in immunotherapy, and an in-depth understanding of treatment-related toxicities have also contributed to the evolving trends in the current management of malignant melanoma patients who have brain metastasis.

## BRAIN RADIATION AND EXTRACRANIAL ABSCOPAL RESPONSES

In the past, the brain has been viewed as an immunologically inert organ and isolated from the central immune system owing to the presence of the blood-brain barrier (BBB).[47,48] The lack of draining lymphatics, the apparent immunoincompetence of microglia, and the resident central nervous system (CNS) macrophage supported the view that the brain was considered to be an immune-privileged organ, fully isolated from the body's immune system by the BBB.[49,50] Autoimmunity and neurodegeneration of the brain were thought to be automatic consequences of immune cell encounter with CNS antigens. In addition, the brain was believed to be composed primarily of tissue from postmitotic cells that were highly vulnerable to the onslaught of activated immune cells when they infiltrated the brain. Thus, regular immune responses from therapeutic interventions were thought to be very limited in the brain. The notion that the brain radiation could induce an extracranial abscopal effect would thus sound particularly unusual because of the traditional view that the brain has its own distinctive immune microenvironment.[47–50] The nascent tumor–associated antigens liberated after brain radiation encounters the hurdle to travel across the BBB.[51] Given the immune privileges of the brain, radiation-induced extracranial abscopal effect was considered to be a particularly unusual event in the treatment of malignant cancers.

Recently, there has been growing interest in reevaluating the type of cellular immune responses that can occur within the brain.[52,53] Emerging data from various studies has significantly altered our earlier understanding that the brain is neither isolated nor passive in its interactions with the immune system.[54] The brain, once viewed as an immune-privileged inert organ and protected by the BBB, is now established as the dynamic immunologic environment.[55] Peripheral immune cells can travel across the intact BBB to prevent and respond to events such as localized infection. Studies have shown that neurons and glia of the brain actively regulate macrophage and lymphocyte responses.[54] However, these macrophages differ from other macrophages or DCs in their ability to direct neuroprotective lymphocyte responses. Moreover, current data indicate that the brain is both immune-competent and actively interacts with the peripheral immune system.[54,56] Furthermore, the brain can recognize inflammation, which is a prominent feature of several neurodegenerative disorders.[57,58] Thus, radiation treatment to 1 or more locations of the brain can induce abscopal responses in tumor sites away from the treated metastatic sites in the brain.

## INTERACTIONS BETWEEN THE BBB AND ABSCOPAL EFFECT

The BBB is the interface between the vasculature and the brain that separates the circulating blood from the brain and extracellular fluid in the CNS.[59,60] The principal function of the BBB is to provide a defense against infections and toxins entering the brain via the bloodstream circulation. Structurally, the BBB is composed of a complex cellular system of highly specialized endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, and pericytes embedded in the capillary basement membrane.[59,60] Together, these cells compose the brain endothelial structure and define the physical properties of the BBB. The cellular and extracellular networks of the highly specialized endothelial cells regulate the transportation of the essential cellular molecules between the extracellular and intracellular compartments. With the highly regulated transportation system, the BBB protects the CNS from the toxic cellular byproducts through the efficient efflux and moving them back into the circulation while permitting the regulated influx of circulating molecules essential for the brain to function normally.[59,60] Thus, the BBB endothelium and neuroparenchymal cells constitute the neurovascular unit, which acts as a "gatekeeper" within the brain that tightly controls the transcellular and paracellular crossing of molecules and cells.

The structural and complex features of the BBB limit the systemic delivery of small and large therapeutic molecules to the brain. Depending on the necessity, both neuronal and non-neuronal cells regulate the expression of transport and tight junction proteins in the endothelial cells, which in turn may "loosen" or "tighten" the BBB.[60,61] The endothelial tight junctions of the BBB plays a critical role in preventing large

molecules such as neurotoxic plasma components, blood cells, and pathogens from entering the brain. Thus, the immune system and the brain share a unique relationship through the CNS. Although the CNS is considered immunologically unique, some populations of immune cells can "loosen" and cross the BBB during neuroinflammation, whereas others can repair damaged nervous tissue.[60,61] The passage of immune cells through the BBB depends on the elaborate cross-talk termed diapedesis, which involves activation of both the immune cells and the BBB cells.[62,63] However, the passage of immune cells through the BBB occurs at low rates under normal physiological conditions.

To maintain the physiological functioning of neuronal cells, the BBB regulates the transport of certain critical small molecules (with a molecular weight < 400 Da and forms < 8 hydrogen bonds) into and out of the CNS through a lipid-mediated free diffusion.[64,65] In addition, various differentially expressed carriers and receptor-mediated systems control the transportation of the larger molecules across the BBB.[64,65] Furthermore, the BBB itself secretes various molecules including cytokines, prostaglandins, and nitric oxide that affect immunologic signaling.[49] Studies using a mouse model have shown that a cell-mediated immune response to foreign antigens in the brain cannot be mounted unless the BBB is disrupted.[66] Under normal physiological conditions, various regulatory components of the BBB prevent immunologic mechanisms of the abscopal effect. If there is a low rate at which the immune cells cross the BBB then it is likely that this would be an insufficient volume of immune cells to produce an abscopal effect observed in clinical cases following radiation therapy. Peptide antigens of suitable size are required to be presented to T cells and are among the smaller elements that can mediate an abscopal response.[64] However, these peptide antigens cannot diffuse freely across the BBB due to the limitations of their size and solubility. As the transport of larger molecules is tightly controlled by the BBB, the tumor-associated antigens are very unlikely to cross in significant amounts through receptor-mediated transportation.

## EFFECTS OF IONIZING RADIATION ON THE STRUCTURAL INTEGRITY OF THE BBB

The BBB, as a specialized neurovascular unit, is a consistent barrier system that protects the healthy brain from toxic substances.[60,61] Therefore, the brain microenvironment can thwart the effectiveness of cancer treatment including radiation therapy against primary brain tumors as well as brain metastases. In normal physiological conditions, the BBB prevents the passage of immunogenic signaling molecules which are essential for the induction of the abscopal effect from the intracranial compartment to the extracranial compartment or vice versa.[67] However, it is now possible that the endothelial permeability of the BBB can be modulated using advanced radiation delivery techniques to facilitate the free passage of the immunogenic signaling molecules between the intracranial and extracranial compartments. Nevertheless, the exact mechanism of ionizing radiation-induced permeability changes in the BBB remains to be established.

Studies have shown that brain radiation modulates the BBB permeability by inducing morphologic changes in its tight junctions, reducing the cell density, and producing the formation of actin stress fibers in cerebral endothelial cells in the healthy regions of the brain.[68,69] Other studies have also shown that brain radiation increases the uptake of labeled markers by modulating the permeability of the BBB.[70] Potential mechanisms for this increased uptake include modulation of the vasculature thereby opening the tight junctions, and increasing the activation of the vesicular transport pathways between the intracranial and extracranial compartments.[69,71,72] Clinical evidence that ionizing radiation modulates the BBB permeability has been suggested by the detection of increased intracranial concentrations of radiolabeled markers and chemotherapy agents after irradiation. For instance, Qin et al[73] observed a linear dose-response when measuring uptake of a technetium marker during radiation therapy in patients with brain tumors. Spatial differences in the uptake of labeled markers between regions that received higher or lower doses of radiation and increased levels of methotrexate in the cerebrospinal fluid have been reported following radiation therapy.[74] These findings form the basis and provide an explanation for why an abscopal effect traversing intracranial and extracranial compartments can be observed after radiation therapy. It is likely that ionizing radiation of tumor lesions not only produces tumor-associated antigens and immunogenic signaling molecules but also facilitates their passage into the extracranial vasculature by modulating the BBB permeability (Fig. 2).

## CLINICAL EVIDENCE OF EXTRACRANIAL ABSCOPAL EFFECT IN METASTATIC MELANOMA

### Search Strategy and Selection Criteria

The main objective of our search was to recover and reanalyze published data on extracranial abscopal effects after the CNS radiation therapy in patients with malignant melanoma. To investigate the role of CNS radiation therapy in the induction of extracranial abscopal responses in malignant melanoma patients, we performed a systematic literature search using electronic databases such as MEDLINE via PubMed and Google Scholar. The combinations of the broad search term "abscopal effect" with any of the association to the following terms was used for the search in the database: radiation, radiotherapy, radiosurgery, radiation therapy, malignant melanoma, brain metastasis, and oncology.

The PRISMA methodology was used for selecting clinical studies published in the peer-reviewed literature based on the following criteria. For the inclusion in this review, we reviewed titles and abstracts of each published articles independently. Full-length articles were retrieved when the abstract was considered relevant and only papers published in English were considered. The bibliographies of retrieved papers and reviews were also sought to identify other relevant articles to be included. Nonindexed journals were manually searched to find clinical evidence for radiation therapy–induced extracranial abscopal effect in patients with malignant melanoma.

Over the past 3 decades, several investigators have reported radiation-induced abscopal effects in cases of patients with malignant melanoma and other cancers. However, radiation-induced extracranial abscopal effects was rarely reported in malignant tumors including malignant melanoma. Emerging clinical data indicate that ionizing radiation has the potential to induce an extracranial abscopal effect in malignant melanoma patients with brain metastasis. Specifically, this extracranial abscopal effect was observed mainly in clinical cases (Table 1) and in small cohort studies (Table 2) when ionizing radiation was delivered to 1 or more locations of CNS metastases of the malignant melanoma.

### Case Reports Showing Extracranial Abscopal Effect

Recently, we reported a case of an extracranial abscopal effect in a female patient with malignant melanoma with brain metastasis.[75] This case involved a 42-year-old female patient who

**TABLE 1.** Summary of Clinical Cases of Extracranial Abscopal Responses Induced by Brain Radiation in Metastatic Melanoma

| Sex | Age (y) | Modality of RT | Total RT Dose and Fractions | Systemic Therapy | Site of Extracranial Abscopal Response | Time to Abscopal Response | References |
|---|---|---|---|---|---|---|---|
| Female | 42 | WBRT | 30 Gy 15 fractions | Dabrafenib/ trametinib | Chest mass and axilla | Within weeks | D'Andrea and Reddy[75] |
| Female | 37 | SRS WBRT | SRS: 24 Gy Fractions not specified WBRT: 30 Gy 10 fractions | None | Skin lesions | Post RT | Galkin et al[76] |
| Female | 36 | WBRT | 20 Gy Fractions not specified | None | Skin lesion | NR | Sperduto et al[77] |
| Male | 67 | WBRT | Not specified | None | Skin lesion | After RT | Okwan-Duodu et al[78] |
| Male | 44 | WBRT | 30 Gy 10 fractions | Ipilimumab | Renal, lung, and liver lesions | 3 mo | Thallinger et al[79] |
| Female | Not specified | SRS | Not specified | Ipilimumab | Pelvis and lung lesions | Post RT | Kiess et al[80] |
| Male | 57 | WBRT | 20 Gy 5 fractions | None | Skin lesion | 2 wk | Teulings et al[81] |
| Male | 49 | SRS | 21 Gy 3 fractions | Ipilimumab | Liver and extremity lesions | Post RT | Ruzevick et al[82] |
| Male | 68 | SRS | Not specified | Vemurafenib | Pelvis and spine lesions | Post RT | Sullivan et al[83] |

NR indicates not reported; RT, radiation therapy; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

was diagnosed with stage III melanoma of her right upper back. At that time, she underwent local surgical excision of her tumor. The patient remained asymptomatic for over 5 years but later she developed a large metastatic lesion in her anterior upper right retropectoral region of the chest wall and right axilla. On the basis of genomic analysis, the patient was treated with molecularly targeted agents such as dabrafenib and trametinib. However, the patient soon developed CNS symptoms due to brain metastasis before the initiation of the molecular targeted therapy. An MRI of her brain revealed at least 8 ovoid enhancing lesions measuring up to 0.9 cm, which were scattered throughout the bilateral cerebral hemispheres and left thalamus compatible with metastatic melanoma. However, a bone scan showed no evidence of osseous metastasis. Later, the patient underwent whole-brain radiation therapy (WBRT) to a dose of 30 Gy delivered in 15 fractions to her multiple CNS lesions. Concurrently, the patient also received gene-targeted therapy with systemic dabrafenib and trametinib. The patient's CNS metastases improved significantly following radiation treatment. A significant reduction in her untreated chest mass was also observed after the CNS radiation treatment indicating an extracranial abscopal effect during the time the patient received cranial radiation therapy. The patient's chest disease was further treated and she was disease-free by imaging. She continued to receive her dabrafenib and trametinib therapy. Unfortunately, the patient developed recurrent disease outside of her previously treated field that quickly became metastatic despite her continued systemic therapy. These findings suggest that the patient experienced an initial extracranial abscopal response during radiation therapy to her brain lesions. Eventually, the patient died due to widespread disease recurrence despite her continued systemic treatment with gene-targeted therapy.

Galkin et al[76] reported a case of an extracranial abscopal effect induced by radiation therapy in a melanoma patient with brain metastasis. The case involved a 37-year-old female who initially underwent surgical resection of her malignant

**TABLE 2.** Summary of Clinical Study Reports of Extracranial Abscopal Responses in Metastatic Melanoma Induced by Brain Radiation

| Study Type | Patients (N) | Radiation Therapy | Total Radiation Therapy Dose | Immunotherapy Agent | Extracranial Abscopal Response, n (%) | References |
|---|---|---|---|---|---|---|
| Prospective | 15 | WBRT/SRS | 30 Gy (WBRT) 20 Gy (SRS) Fractions not specified | Ipilimumab | 3 (20) | Theurich et al[84] |
| Retrospective | 16 | WBRT/SRS | 36 Gy (WBRT) 22 Gy (SRS) Fractions not specified | Ipilimumab | 10 (63) | Schoenfeld et al[85] |
| Prospective | 13 | WBRT/SRT | 30 Gy (WBRT) 10 fractions 20-24 Gy (WBRT) 1 fraction | Ipilimumab | 7 (54) | Grimaldi et al[86] |

SRS indicates stereotactic radiosurgery; SRT, stereotactic radiation therapy; WBRT, whole-brain radiation therapy.

melanoma in the sacrum area. A year later, an inguinal-femoral lymphadenectomy was performed due to disease progression at that site. One year after the lymphadenectomy, her MRI evaluation revealed multiple relatively small brain metastases without edema and mass effect. The patient underwent SRS to the target lesions in her brain to a total radiation dose of 24 Gy. A follow-up MRI 6 months later 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 the new and recurring brain lesions with the marginal treatment dose of 20 and 24 Gy to the lesions. 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, the patient received another course of SRS with the mean dose of 20.3 Gy to a prescribed dose of 18.5 Gy to her lesions. Two months after the CNS radiation, the patient experienced a partial response of several irradiated lesions and stabilization of other nonirradiated lesions. However, 14 months later, the patient experienced disease progression, which was manifested by the emergence of new metastases. At that point of time, the patient received another course of SRS with a marginal dose of 24 Gy to the treated lesions. However, the patient 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 a clinical and radiographic improvement. In addition, the regression of her aphasia and hemiparesis was seen. Moreover, the patient had an improvement in her cognitive function and diminishing of intradermal lesions over 4 months period. Furthermore, the patient had partial regression of the 10 metastases that emerged after the last radiosurgery. However, 13 months later the patient experienced new recurrent disease for which the patient again underwent SRS, followed by WBRT which provided prolonged survival of 49 months from brain metastases detection. Overall, the patient's radiation therapy produced an extracranial abscopal effect in the form of the disappearance of nonirradiated intradermal lesions without any systemic therapy.

Sperduto et al[77] have reported a case of an extracranial abscopal effect of radiation therapy in a 36-year-old female melanoma patient with multiple brain metastases. The patient initially presented with a tumor mass on her right neck which was later confirmed as malignant melanoma. The patient received radiation therapy to a total radiation dose of 64 Gy to the left neck and scalp followed by 3 cycles of cisplatin, interferon, and vinblastine and then IL-2. However, 8 months later the patient developed a hypermetabolic nodule in the retroperitoneum consistent with metastatic recurrence as well as brain metastasis. The patient underwent SRS to all 3 metastatic brain lesions and then stereotactic ablative radiation therapy was added to the pelvic soft tissue metastasis (25 Gy, 5 fractions over 2 wk) 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 metastases and > 10 years after completion of her other treatment. The authors concluded that the treatment course was consistent with emerging literature on the extracranial abscopal effect of radiation therapy.

In a case study by Okwan-Duodu et al,[78] it was shown that ablative radiation therapy in combination with immunotherapy was effective and produced an extracranial abscopal response in a 67-year-old male patient who presented with metastatic melanoma. The patient had the initial diagnosis of advanced metastatic melanoma with the brain, subcutaneous tissue, mesenteric, pelvic, and retroperitoneal involvement. He was treated initially with SRS without a significant response. The patient then underwent WBRT in combination with IL-2 immunotherapy. The patient responded well to the combination therapy suggesting that the combination of radiation therapy with immunotherapy had a synergistic effect in controlling the metastatic melanoma.

Thallinger et al[79] reported a case of an extracranial 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 metastatic melanoma to the lung, liver, kidney, and adrenal glands. The molecular analysis of the patient's melanoma biopsy showed that there were no mutations seen. 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. Follow-up evaluation showed complete resolution of not only the radiation treated brain lesions but also the untreated renal lesions, along with partial regression of both liver and lung lesions. The complete remission of the untreated renal metastatic lesions as well as the partial regression of both the liver and lung metastatic lesions demonstrated the evidence for the extracranial abscopal effect of radiation therapy.

In a retrospective analysis of their institutional melanoma database, Kiess et al[80] reported a case of the extracranial 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, the patient was administered radiation therapy to her brain lesions using SRS. A follow-up evaluation indicated that the patient experienced a gradual durable response in the pelvis and lungs following her brain SRS. The patient remained on ipilimumab therapy for 2 more years without disease recurrence. Thus, this case demonstrated that the 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 extracranial abscopal response.

Teulings et al[81] reported that treatment with radiation therapy induced an extracranial abscopal response in a malignant melanoma patient with brain metastasis. This case study included a 67-year-old male who experienced depigmentation within the target volume several weeks after completing axillary radiation therapy (60 Gy, 30 fractions). Several months later, the patient developed brain metastases. Two weeks after completing a course of WBRT (20 Gy, 5 fractions), the patient developed depigmentation within and outside of the target volume, at sites not previously irradiated suggesting an extracranial 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. Moreover, the Immunologic analyses of the patient's peripheral blood as well as the biopsies of depigmented skin and metastatic lesions showed the presence of specific CD8$^+$ T-cell and B-cell responses against melanocyte differentiation antigens.

Ruzevick et al[82] reported an interesting case of the extracranial abscopal effect in a melanoma patient with brain metastasis and human immunodeficiency virus. The case involved a 48-year-old white male who underwent a highly active antiretroviral therapy for his human immunodeficiency virus-acquired immunodeficiency syndrome. Two years later, the patient developed a progressive, left-sided facial, upper extremity, and lower extremity numbness, which was

subsequently confirmed as metastatic melanoma upon pathologic evaluation. Following surgery, the patient received immunotherapy using ipilimumab and SRS boost to the tumor bed in the brain to a total dose of 21 Gy delivered in 3 fractions. However, 2 more new brain metastatic lesions were observed in the patient: 1 metastatic lesion being in the right occipital lobe and another in the left frontal lobe. Both brain metastases were treated with the second course of SRS delivered to ta total dose of 20 Gy in a single fraction. Despite the treatment with radiation, the patient developed 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 the post-SRS inflammation and not the true progression of the underlying disease. A follow-up evaluation after 6 months showed stabilization of the patient's brain metastases while interval positron emission tomography/computed tomography imaging showed stabilization or complete resolution of the untreated distant lesions indicating the extracranial abscopal effect due to the radiation therapy.

In an interesting case from Massachusetts General Hospital, Sullivan et al[83] described a case of an extracranial abscopal effect of radiation treatment in a melanoma patient with brain metastasis. The patient was a 63-year-old male with metastatic melanoma, who was positive for the BRAF V600E mutation. Initially, the patient was found to have metastatic lesions in the retroperitoneum, pelvic sidewall, and right inguinal lymph nodes (largest lesion, 4 cm in size). The patient 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. Owing to drug intolerance, vemurafenib therapy was discontinued and the patient received SRS to the single brain lesion. The patient was offered to have other treatments but elected not to receive any further treatment. A follow-up evaluation 1 year after his radiation therapy showed not only a complete resolution of his treated brain lesion but also the regression of his untreated bone and inguinal lymph node lesions. Further follow-up evaluation after 1.5 years of the completion of his treatment showed no evidence of disease indicating the extracranial abscopal effect of radiation therapy.

## Cohort Studies Showing Extracranial Abscopal Effect

Theurich et al[84] analyzed clinical data from 127 melanoma patients, including 45 patients treated with ipilimumab and radiation therapy. The addition of radiation therapy to ipilimumab significantly prolonged the median overall survival (93 vs. 42 wk, $P = 0.0028$) of the patients. Of the patients who received the treatment, 15 had CNS radiation therapy. Of these 15 patients, 3 (20%) experienced measurable extracranial abscopal responses. Importantly, the extracranial abscopal responses were mainly seen at the pulmonary metastatic sites. A multivariate Cox regression analysis showed that the effect of added radiation therapy on the patients' overall survival remained statistically significant ($P = 0.05$). Overall, these results suggest that brain radiation can induce extracranial abscopal effects in patients with malignant melanoma.

Schoenfeld et al[85] analyzed 16 melanoma patients who received SRS to their brain metastases and ipilimumab therapy and systematically evaluated their extracranial abscopal responses by following the largest extracranial lesion. The extracranial index lesions were decreased in size within 3 months after the brain-directed radiation therapy in 10 (63%) of the 16 patients. The median overall survival was longer for patients (17 mo) who initially were treated with SRS compared with all patients (14 mo). Thus, these findings indicate that brain radiation can induce extracranial abscopal effects in patients with malignant melanoma.

Grimaldi et al[86] analyzed 21 advanced melanoma patients who progressed even after treatment with ipilimumab therapy. Of these 21 patients, 13 (62%) received WBRT/SRS for the brain, 4 bone, 2 distant lymph nodes, and 2 cutaneous metastases. Of the 13 patients who received brain radiation therapy, 7 (54%) experienced extracranial abscopal responses which were evidenced by the regression of cutaneous, chest wall, gastric, liver, lung, lymphnodal, and retroperitoneal abdominal metastatic lesions. In addition, 4 (50%) of the 8 patients who received radiation therapy at extracranial sites also experienced abscopal responses. Overall, 11 (53%) of the 21 patients experienced abscopal responses after radiation therapy. Among those patients who experienced abscopal response, 9 had partial responses and 2 had stable disease. The median overall survival for all 21 patients was 13 months. The median overall survival was longer for patients who experienced the abscopal response (22.4 vs. 8.3 mo, $P = 0.02$). Collectively, these findings add to this growing body of evidence that brain radiation can induce extracranial abscopal effects in patients with malignant melanoma.

## CONCLUSIONS

The current literature describes several clinical cases of extracranial abscopal effects following radiation therapy for 1 or more intracranial metastases from malignant melanoma. Clinical evidence suggests that an abscopal effect induced by brain radiation therapy can cross the BBB and triggers tumor regression in the nonirradiated extracranial locations. Furthermore, evidence from these studies indicates that radiation therapy disrupts the integrity of the BBB allowing the abscopal signaling molecules to pass across from the intracranial to extracranial compartments and vice versa to achieve distant abscopal responses. However, most patients included in these studies had been treated with systemic immunotherapy in addition to radiation. Therefore, it is not clear if these clinical responses represent the abscopal effect was solely from radiation therapy alone or a response from the combination of radiation given with systemic immunotherapy.

In general, it is currently challenging to distinguish true distant responses from either radiation therapy or from the combination of other systemic anticancer treatment, especially when evaluating the abscopal effect. However, it is possible to assess those immunostimulatory changes that are required to mediate the abscopal effects induced by radiation therapy in the absence of systemic therapy. For example, measurements of titers of tumor-specific antibodies can provide evidence for true abscopal effects from radiation therapy. However, when radiation therapy is combined with systemic immunotherapy, it is more difficult to identify if the abscopal responses are from one or the other or both modalities. If the abscopal effect is a result of the antitumor immune response enhanced by radiation therapy, then one must effectively distinguish between the outcomes of 2 different immunologic therapies. In addition, by stratifying the timing of systemic immunotherapy in relation to when radiation therapy is delivered, it may be possible to distinguish the effects between these 2 modalities. Despite the current challenges in measuring true abscopal effects, the critical role played by radiation therapy needs to be recognized, especially in its ability to liberate tumor-associated antigens from dying tumor cells and disrupting the BBB that allows communication between the intracranial and extracranial compartments.

Given the limited data available on the extracranial abscopal responses to radiation therapy in world literature, the issue remains open and prospective data is needed to gain definitive evidence about it. Indeed, the increasing treatment options for metastatic melanoma, including novel strategies of immunotherapy, require urgent clarification of interactions with radiation therapy, whose effect may be crucial to optimize the outcome of melanoma patients with brain metastasis. Moreover, these strategies should also exploit the combined use of radiation therapy and immunotherapy in different protocols such as timing, sequential, or concurrent therapies in relation to the induction of extracranial abscopal responses in metastatic melanoma patients. It should be noted, however, that the radiation dose and fractionation regimen optimized for a robust local tumor response might be different from that optimized for a distant extracranial abscopal response. Nonetheless, additional studies are required to increase the knowledge base of the extracranial abscopal effect induced by radiation therapy in melanoma patients with brain metastasis.

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