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The systemic immunostimulatory effects of radiation therapy producing overall tumor control through the abscopal effect

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Abstract

Objective Emerging studies show that radiation therapy produces an important out of field (distant) effect known as the "abscopal effect" in nonirradiated tumor sites. The objective of this study was to provide an overview of the current state of knowledge and clinical experience of radiation therapy producing abscopal effects in the management of different types of malignant diseases.

Methods Peer-reviewed published clinical evidence on the abscopal effect of radiation therapy was collected using electronic databases such as Medline via PubMed and Google Scholar. The reference lists were searched in the publications that we obtained in an attempt to find additional relevant publications. Non-indexed peer-reviewed journals were manually searched and relevant information was extracted. The search was restricted to English language articles. The clinical data on the abscopal effect of radiation therapy were reviewed and the outcomes have been summarized.

Results Currently, only clinical case reports and anecdotes have slowly converted into solid clinical data and interest is building in the field of radiation therapy, specifically on how local radiation can produce the abscopal effects for the management of different types of malignant tumors. Extensive clinical evidence suggests that the radiation therapy induced abscopal antitumor effects are mediated by immune cells such as the T-lymphocytes. This forms a basis for using radiation therapy in combination with immunotherapy to augment the abscopal response rates in cancer patients. Current evidence demonstrates that radiation therapy induces abscopal responses across many tumor types.

Conclusion Together, the clinical outcomes from published reports suggest that localized radiation therapy is capable of inducing abscopal effects in a wide variety of malignant tumors. With the advent of novel immunotherapies, the potential for immune activation by radiation defines a novel role for radiation therapy in the treatment of systemic disease. A clinical consideration of the abscopal effects produced by radiation therapy could lead to a revolutionary change in the current management of patients including radiation treatment strategies and immunotherapies for various malignant tumors.

Keywords Abscopal effect · Immunomodulation · Malignant tumors · Metastasis · Radiation therapy · Solid tumors · Systemic effects

Introduction

Radiation therapy plays a crucial role in the treatment of a multitude of malignancies. Approximately 60% of all newly diagnosed cancer patients will receive radiation therapy with a curative intent or in a palliative setting [1–3]. Conventional external beam radiation therapy doses that are effective at controlling local tumor growth are delivered in multiple small daily doses, over several weeks. However, innovations in radiation therapy technologies have allowed the delivery of highly conformal radiation beams with increased precision while sparing the adjacent normal tissue. In addition to this, the advent of sophisticated imaging methods together with novel irradiation devices has led to the development of three-dimensional (3D) conformal radiation therapy, which uses 3D based beams to deliver higher doses of radiation. Other innovative techniques such as stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT) have transformed the delivery of radiation and broadened its range of clinical applications.

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Traditionally, the antitumor effects of radiation therapy were believed to be immunosuppressive; however, current evidence suggests that radiation therapy has potent immunomodulatory effects, by enhancing tumor immunogenicity and augmenting antitumor responses both locally and systemically [4]. While advances in radiation therapy technologies have largely focused on minimizing adverse local toxicities and optimizing the clinical benefits when treating localized tumors, recent investigations have aimed to increase the immunomodulating effects that provide a promising frontier in extending the use of radiation therapy to treat both localized and metastatic diseases. In the recent past, studies have shown that the immunomodulating effects of radiation therapy involve stimulating the local immune system, which alters the immunosuppressive tumor microenvironment. Alterations in the microenvironment then prompt reactivation of the immune response, a phenomenon called an abscopal effect of radiation therapy. The abscopal effect of radiation was originally described by Mole in 1953. He noted that localized radiation targeted at a malignant tumor triggered systemic antitumor effects [5]. The term *abscopal* effect derived from the Latin ab (position away from) and scopus (target or mark). This is also referred to as the "distant bystander effect" and implies that radiation therapy has not only a locolized action on the target tumor tissue but also an out-of-field systemic antitumor effect [6].

Despite the fact that the abscopal effect of radiation has been known for decades, its existence was only rarely described in sporadic case reports. However, recent advances in the understanding of the immunomodulating effects of radiation have provided a renewed interest in investigating its distant antitumor effects thereby leading to additional clinical benefits in a variety of malignancies. Several case studies have shown that the abscopal effects of radiation therapy have been mostly observed in immunogenic tumors such as melanoma, kidney, lung, and hepatic cancers [7]. However, recent novel developments of immunotherapeutic strategies combining targeted immunomodulating systemic agents and immune checkpoint inhibitors with radiation have shown that the abscopal effect can be seen in both solid and hematological malignancies. Accumulating evidence suggests that these systemic combinations may complement each other's therapeutic impact and offer greater clinical efficacy in the treatment of both localized and metastatic cancers. In this review article, we provide an overview of the current state of knowledge and clinical experience of the abscopal effect of radiation therapy.

A historical perspective of radiation therapy

The history of the use of radiation in medicine can be divided into four eras: the initial discovery era; the orthovoltage era; the megavoltage era; the new millennium era. During the initial discovery era, the fundamentals of radiation were established. In this era, Wilhelm Conrad Rontgen [8] discovered X-ray in 1895, although X-rays were produced earlier by others unwittingly. The discovery of X-ray was soon followed by Becquerel's report [9] on the phenomenon of radioactivity in 1896, and Madam Curie's discovery of radium as a source of ionizing radiation [10]. These discoveries paved the way for various novel radiation techniques such as teleradiotherapy, using a long source-to-surface distance (SSD), and later called external beam radiation therapy (EBRT), and brachytherapy, based on short SSD that is implanted into tissues and is delivered with radium needles or surface molds [11].

In 1901, Becquerel and Curie reported on the physiologic effects of radium rays. During the first decade of the twentieth century, interest in studying the clinical use of X-rays increased and a number of studies reported its use in the treatment of skin cancers [12]. In the 1910s, Coolidge developed a new device able to emit higher energy X-rays, to treat deeper cancers [13]. It was only by the 1920s that a better understanding occurred about the biological effects and the total radiation dose and the importance in the fractionation of radiation for the treatment of malignant diseases. To understand the physical properties of X-rays and their biological effects, X-rays were used by Emil Herman Grubbe to treat a patient with breast cancer [14]. In addition to the discovery of X-rays, increased knowledge of gamma rays and the structure of the atom and its orbits with electrons, protons, and neutrons occurred to close out the first era.

The orthovoltage era encompassed the late 1920s to 1950s in which a major achievement was made to measure the radiation dose using ionizing chambers with the development of the first accurate dose unit (the Röntgen unit) in 1932 [15]. In this era, the treatment of deep tumors was better addressed using radium-based intracavitary and interstitial irradiation (brachytherapy) due to the absence of deeply penetrating external beam sources. New developments in external beam therapy took place during this era leading to super voltage (approximately 500 kV–2 MV) radiation therapy which was made during this era. In the 1940s, electron beam acceleration became practical and useful as therapeutic options in radiation medicine. The first device was developed with 2 MeV electrons and subsequently, later devices yielded up to 300 MeV. In the mid-1940s, synchrotron devices were developed which allowed the energy of acceleration to be varied so that a deeper penetration of radiation into the tissue for optimal cancer treatments could be achieved [16, 17].

The successive period, from the 1950s to 1990s, was regarded as the era of megavoltage radiation in which studies focused primarily on the development of innovative radiation therapeutic devices that could be used for the treatment of complex tumors located in the deep tissues. This era witnessed the introduction of the Cobalt teletherapy, generating high-energy γ-rays, and later more potent electron linear accelerators, able to deliver deeply penetrating megavoltage X-rays. The 1970s and 1980s witnessed the introduction of innovative devices delivering proton beams and computer-assisted accelerators for photons that were successfully applied to treat different kinds of tumors. During this era, the efficacy and modern methods of delivering radiation therapy were demonstrated in well-designed clinical trials, the practice of radiation oncology became an independent and well-recognized medical discipline in cancer therapy, and the first radiation oncology associations were founded [16, 17].

The new millennium era has been characterized by major innovations in radiation therapy which have evolved since the late 1990s [16–18]. An important progress in radiation therapy was achieved by the introduction of more advanced three-dimensional conformal radiation therapeutic devices and treatment planning systems as well as stereotactic radiation therapy that was more effective, especially for the treatment of complex and irregularly shaped tumors. These advances together with the development of highly sophisticated radiation therapy treatment planning systems have led to the introduction of novel treatment techniques to apply precise radiation to malignant tumors. These include intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy y (IGRT) which have transformed the delivery of radiation to the tumor and the overall broadening the range of the applications of radiation therapy.

Mechanism of the abscopal effect

Historically, the clinical role of radiation therapy has been primarily focused on controlling and eradicating local disease by maximizing direct tumor cell damage while sparing the surrounding healthy tissues. The tumor cell death has been attributed to the ability of radiation to induce DNA damage leading to the eradication of local disease [19]. However, recent technological advances in accurate, high-dose radiation delivery have permitted the feasibility of its use to control the systemic burden in some cases of metastatic cancer. Evidence suggests that the abscopal effect is a consequence of the immunomodulating effects of radiation in the tumor microenvironment through the clearance of tumors via diverse cell-killing mechanisms (Fig. 1) [20].

The complex mechanism behind the therapeutic abscopal effect is not completely understood, but immune-mediated cell death is thought to be a main component of the event. The immunomodulating effect of radiation is supported by several studies which have elucidated how combining radiation with immunotherapy can boost this effect. It is believed that the off-target effects of radiation at non-irradiated distant tumor sites are mediated by tumor antigen–primed T lymphocytes (T cells)

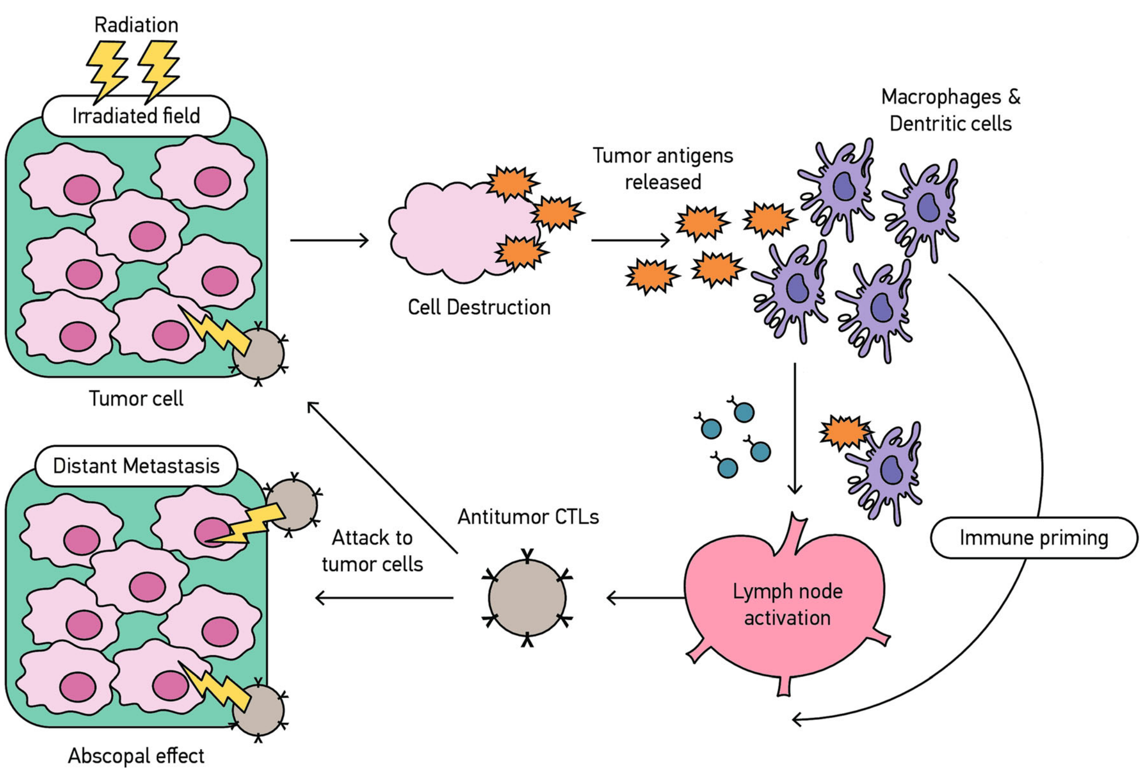

Fig. 1 Schematic drawing of the mechanism of the radiation therapy–induced abscopal effect in various malignant tumors. Irradiation of the tumor causes tumor cell destruction and initiation of the immune process by liberating tumor antigens and producing damage-associated molecules, which lead to the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

that travel to metastatic sites and promote tumor regression. It is hypothesized that radiation leads to the liberation of tumor antigens and the production of damage-associated molecules, which lead to the maturation of dendritic cells and T cell priming in an immunogenic context [20]. In this process, the release of tumor antigens acts as pro-inflammatory mediators, stimulating monocyte production of the cytokines such as tumor necrosis factor, interleukin-1 (IL-1), IL-6, and IL-8. Collectively, these events promote tumor cell elimination by primed T cells. The relative importance of these alterations caused by radiation in the tumor microenvironment is still unclear; however, it is believed that the immune system senses this damage and triggers immune response pathways resulting in several areas of systemic stimulation [21]. 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 [22]. This can induce and improve an immune response specific to the tumor cells [23]. There is now a growing consensus from many studies indicating that combining radiation therapy with immunotherapy provides an opportunity to boost abscopal response rates.

Clinical evidence

A systematic literature review was performed in order to find published clinical evidence, primarily in the peer-reviewed literature using electronic databases such as MEDLINE via PubMed and Google Scholar. The combinations of the key word "abscopal effect" with any of the association to the following terms were used for the search in the database: radiation therapy, advanced cancer, malignant tumors, metastasis, systemic effects, 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. Non-indexed journals were manually searched. The search was restricted to English language articles.

Clinical evidence of abscopal effects in response to radiation has been reported since the early 1970s. However, most of the evidence of the abscopal effects of radiation has been in the form of case reports (Tables 1, 2, 3, 4, and 5) [24–75] and small nonrandomized studies [76, 77]. The clinical outcomes of these reports serve as a basis for the development of innovative approaches for the treatment of various malignancies. In early reports, the abscopal effect following radiation has been demonstrated in immunogenic tumors such as melanoma, hepatic, renal, and lung cancers. Innovations in immunotherapeutic strategies which combine targeted immunomodulating agents and immune checkpoint inhibitors with radiation have revealed that the abscopal effect is more promising in both solid tumors and hematological malignancies.

Abscopal effects in lung cancer

There is a growing body of evidence that has emerged from published case studies supporting the abscopal effects of radiation therapy in metastatic lung cancer (Table 1). Recently, Bitran and colleagues [24] reported on a case of the abscopal response in a patient with metastatic lung cancer treated with local radiation therapy. The patient presented with a stage IV adenocarcinoma of the left lung with a large metastatic left adrenal lesion. Local radiation therapy to a dose of 27 Gy was delivered in 9 fractions to the left lung followed by immunotherapy with nivolumab. Follow-up evaluation showed that the left adrenal metastatic lesion regressed significantly indicating the abscopal effect of the radiation therapy.

Kim and Kim [25] described the abscopal resolution of liver metastasis in a patient with a primary non-small cell lung cancer. The patient also had unresectable cholangiocarcinoma. After a failed initial chemotherapy, the patient received stereotactic body radiation therapy to a dose of 48 Gy delivered in 4 fractions to the right upper lobe non-small cell lung cancer mass. After 3 months post-radiation therapy, the patient showed a spontaneous and complete regression of the metastatic liver lesions indicating the abscopal regression due to radiation therapy.

Lin and co-investigators [26] reported recently on a case of the abscopal effect after delivering stereotactic brain radiation therapy as a second-line treatment in a patient with lung adenocarcinoma. The patient was initially diagnosed with poorly differentiated stage IV adenocarcinoma in the right lobe of the lung. Initial chemotherapy with paclitaxel and nedaplatin failed and the patient's primary tumor enlarged. The patient later underwent immunotherapy with atezolizumab. Although the primary tumor and mediastinal lymph nodes were reduced after immunotherapy, the patient developed metastasis to the brain in the right parietal lobe. Stereotactic brain radiation therapy was administered to a dose of 48 Gy in 8 fractions and immunotherapy with atezolizumab was continued. Three months after radiation therapy to the brain, the nodules in the basal segment of the right lower lung had shrunk and the number of subpleural lesions in the basal segment of the left lower lung had reduced in size. In addition, multiple lymph nodes in the mediastinum had become smaller. These findings indicated the clinical evidence for the abscopal responses of radiation therapy.

Hamilton et al. [27] reported an abscopal effect after radiosurgery for solitary brain metastasis in a patient with advanced non-small cell lung cancer (NSCLC). The patient had a poorly differentiated NSCLC with a brain metastatic lesion. The patient underwent radiosurgery to the solitary brain lesion. A total peripheral dose of 25 Gy was delivered in 5 fractions. One month following brain radiation therapy, a reduction in lesion size was observed in the brain. After 2 months post-treatment, a complete resolution of the original left upper lobe pleural-based mass was noticed indicating the abscopal response of the radiation therapy.

Table 1 Summary of clinical case reports of abscopal effect of radiation therapy in lung cancer

Patient		Primary treated? (yes/no)	Total radiation dose (Gy)	Radiation daily dose and fractions	Site with abscopal effect	Time to abscopal response	References
Gender	Age (years)						
Female	62	Yes, lung tumor mass	27	3Gy, 9 fractions	Adrenal mass	6 months	Bitran et al., 2019 [24]
Male	70	Yes, lung tumor mass	48	12 Gy, 4 fractions	Liver metastatic lesions	3 months	Kim and Kim 2019 [25]
Male	71	No, metastatic brain tumor	48	6 Gy, 8 fractions	Nodules in the basal segment of the right lower lung	3 months	Lin et al., 2019 [26]
Male	47	No, metastatic brain tumor	25	5Gy, 5 fractions	Lung tumor	3 months	Hamilton et al. 2018 [27]
Male	47	No, abdominal lymph nodes	18	2 Gy, 6 fractions	Non-irradiated lymph node	2.5 months	Britschgi et al. 2018 [28]
Female	64	No, paramediastinal foci	37.5	7.5 Gy, 5 fractions	Pulmonary lesions	10 months	Cong et al., 2017 [29]
Male	63	No, metastatic brain tumor	45	3 Gy, 15 fractions	Lung and mediastinal lymph node	9 months	Katayama et al., 2017 [30]
Female	67	No, calvarial metastasis	30	3 Gy, 10 fractions	Skin nodules	1 month	Cummings et al., 2017 [31]
Male	60	No, liver lesions	40	2 Gy, 20 fractions	Non-irradiated primary tumor and other metastatic lesions	3 weeks	Komatsu et al. 2017 [32]
Male	64	No, liver lesions	30 Gy	6 Gy, 5 fractions	Distant sites	3 months	Golden et al., 2013 [33]
Female	78	Yes, lung tumor mass	60	2 Gy, 30 fractions	Outside of the radiation field	2 months	Siva et al., 2013 [34]
Male	72	Yes, lung tumor mass	NR	NR	Metastatic lesions	NR	Yoon et al., 2012 [35]

NR not reported

Britschgi and co-investigators [28] described a case of a metastatic non-small cell lung cancer patient who had a complete response secondary to an abscopal effect of stereotactic body radiation therapy delivered in combination with anti-programmed cell death protein 1 (PD-1) immunotherapy with nivolumab. Following the progression with the nivolumab therapy, the patient received stereotactic body radiation therapy to a dose of 18 Gy delivered in 6 fractions to two of the three lymph node metastatic lesions while continuing immunotherapy. Ten weeks post-radiation therapy, a complete radiological and metabolic response was seen in not only the irradiated lymph node metastatic lesions but also in the non-irradiated lesion of the third lymph node revealing the abscopal effect of radiation therapy.

Cong et al. [29] reported an abscopal response in a patient with metastatic NSCLC. Following the diagnosis of NSCLC, after a failed first-line chemotherapy with cisplatin and pemetrexed, the patient received gefitinib therapy. In addition, the patient received the first dendritic cells and cytokine-induced killers (DC-CIK) immunotherapy. However, the patient showed a marked tumor progression in the lung. The patient then received stereotactic ablative radiation therapy (SABRT) to a dose of 37.5 Gy in 5 daily fractions for the paramediastinal foci. A follow-up chest X-ray performed 10 months after completion of SABRT showed a complete regression of pulmonary lesions suggesting an abscopal response of radiation therapy.

Katayama and colleagues [30] reported the abscopal effects of radiation therapy in a patient with metastatic NSCLC. This patient underwent whole brain radiation therapy (WBRT) plus a boost of radiation therapy to a total dose of 45 Gy delivered in 15 fractions. The metastatic brain tumor presented with cerebral edema from the left temporal lobe to the occipital lobe rapidly progressed after the enucleation of their brain tumor. The patient also received palliative radiation (30 Gy in 10 fractions) for a third lumbar vertebral metastasis. The tumor in the left upper lobe of the lung and his mediastinal lymph nodes had regressed in size indicating the abscopal effects of radiation therapy. Furthermore, these authors concluded that the abscopal effect can occur after the irradiation of metastatic lesions without chemotherapeutic or immunotherapeutic interventions. Cummings and co-investigators [31] have also recently demonstrated that palliative radiation exerted the abscopal effect of radiation therapy in a patient with neuroendocrine atypical carcinoid lung cancer. In this case, the patient underwent palliative radiation with 30 Gy delivered in 10 fractions targeted to a symptomatic calvarial metastasis. One month after radiation, she noted a rapid improvement in her skin nodules suggesting the abscopal effects of radiation therapy. The patient had a durable complete response post-radiation even after 18 months had passed.

Komatsu and co-investigators [32] reported on a case of the abscopal response in a lung cancer patient who progressed on immunotherapy with nivolumab. Initially, the patient had a right upper lobectomy with combined resection of the parietal pleura and part of the right lower lobe along with a mediastinal lymph node dissection after neoadjuvant chemoradiation therapy. However, 6 months after the lobectomy, the patient developed a solitary liver metastasis and an intrapulmonary metastasis. The patient was then placed on unsuccessful nivolumab therapy. The patient was then treated with radiation therapy to a dose of 40 Gy delivered in 20 fractions to the liver metastatic lesions. Three weeks post-radiation therapy, the patient's tumor size showed a remarkable reduction as did the intrapulmonary metastatic lesions distant from the radiation field demonstrating the abscopal response of the radiation therapy.

Golden and colleagues [33] also reported the abscopal effect of radiation therapy in a patient with chemotherapy-refractory metastatic adenocarcinoma of the lung. The patient had progressive liver and bone metastases and was treated with ipilimumab followed by fractionated radiation therapy. The patient had an objective response at all disease sites and had no evidence of disease a year after treatment. Thus, this report found that hypo-fractionated radiotherapy induces abscopal responses when combined with checkpoint inhibitor therapy. Furthermore, the clinical outcomes of this case support that a combination of local radiotherapy and immunotherapy appears to be a useful strategy to improve the outcomes of patients with metastatic NSCLC who were historically known to have dismal prognoses.

Siva et al. [34] reported an abscopal response in a patient with synchronous primary lung cancer. In this case, the patient had chemoradiation to the bulky left-sided primary lung adenocarcinoma, approximately 5 months prior to the delivery of stereotactic ablative radiation therapy (SABRT) to the right-sided lung. Within 2 weeks of SABRT delivery, previously undetected metastatic progression was discovered. Five months following the delivery of SABRT, an abscopal response was observed with the disease regression at adrenal and humeral metastatic sites. Yoon and Lee [35] described a case of abscopal effect with multiple metastatic NSCLC. In this case study, the patient was treated with fractional radiation therapy, modulated electro-hyperthermia, and granulocyte colony-stimulating factor (G-CSF) while expecting an abscopal effect from the treatment. Following the completion of the radiation treatment, the patient experienced nearly complete remission in the multiple metastatic lymph nodes, which were distantly away from radiation therapy field. The outcomes from this case study suggest a successful abscopal effect with local radiation therapy in combination with oncothermia and G-CSF immune-stimulation.

Abscopal effects in melanoma/skin cancer

Several case studies have been reported abscopal effects of radiation therapy in patients within metastatic melanoma (Table 2). In a recent melanoma case study report, Tsui and

Table 2 Summary of clinical case reports of abscopal effect of radiation therapy in melanoma/skin cancer

Patient		Primary treated? (yes/no)	Total radiation dose (Gy)	Radiation daily dose and fractions	Site with abscopal effect	Time to abscopal response	References
Gender	Age (years)						
Female	65	Yes, primary tumor	24	8 Gy, 3 fractions	Lung lesions	After radiation	Tsui et al., 2018 [36]
Female	57	No, oligometastasis	50	10 Gy, 5 fractions	Non-irradiated lesions	3 months	Sims-Mourtada et al., 2018 [37]
Male	84	Yes, primary tumor	39	NR	Lung lesions	3 months	Komori et al., 2018 [38]
Female	36	No, whole brain	25	5 Gy, 5 fractions	Non-irradiated melanoma lesions	18 months	Sperduto et al., 2017 [39]
Female	84	Yes, primary tumor	60	3 Gy, 20 fractions	Non-irradiated melanoma lesions	4 months	Fujimura et al., 2017 [40]
Female	84	Yes, primary tumor	70	3.5 Gy, 20 fractions	Non-irradiated melanoma lesions	4 months	Fujimura et al., 2017 [40]
Male	50	No, whole brain	NR	NR	Metastatic lesions	After radiation	Okwan-Duodu et al., 2015 [41]
Male	57	Yes, axilla and suprascapular region	50	1.7 Gy, 30 fractions	Lung lesions	2 weeks	Teulings et al., 2013 [42]
Male	67	Yes, primary tumor	24	8 Gy, 3 fractions	Metastatic lesions	8 months	Stamell et al., 2013 [43]
Female	33	No, paraspinal lesion	28.5	9.5 Gy, 3 fractions	Spleen lesions	4 months	Postow et al., 2012 [44]
Male	57	Yes, arm	50.4	2.52 Gy, 20 fractions	Arm	6 months	Hiniker et al., 2012 [45]
		No, liver lesions	54	18 Gy, 3 fractions	Liver		
Male	28	No, inguinal region	14.4	1.2 Gy, 12 fractions	Para-aortic lesion	9 months	Kingsley et al., 1975 [46]
Male	84	Yes, skin	40	5 Gy, 8 fractions	Non-irradiated pulmonary disease	2 months	Orton et al., 2016 [47]
Male	70	No, skin	12	6 Gy, 2 fractions	Skin	1 month	Cotter et al., 2011 [48]

NR not reported

colleagues [36] had demonstrated that palliative local radiation therapy (24 Gy, 3 fractions) not only controlled the primary tumor growth but also produced regression of metastatic lung lesions suggesting the abscopal effect of radiation therapy. Sims-Mourtada and co-investigators [37] also showed the abscopal effects of radiation in a patient with oligometastatic melanoma undergoing concurrent treatment with pembrolizumab and stereotactic body radiation therapy. Following the combination treatment with radiation plus pembrolizumab, the patient experienced both local as well as a systemic response as evidenced by an out-of-the radiation field improvement. In another recent case study, Komori et al. [38] reported that radiation therapy when combined with immunotherapy agents such as nivolumab or ipilimumab exerted a booster effect on the immune responses to the tumor in a patient with metastatic melanoma. Sperduto and co-investigators [39] have also shown that when a melanoma patient with multiple brain metastases was treated with radiation therapy followed by chemotherapy, the abscopal effect was observed. The patient experienced remarkable improvement in tumor growth control and remained free of disease for over 10 years after the completion of treatment.

In another study, Fujimura et al. [40] described the abscopal effects of radiation therapy using two cases of multiple in-transit metastatic melanomas. Both cases were treated with IMRT in combination with ipilimumab or nivolumab. After 3–4 months of therapy, both cases had no further development of in-transit metastasis for several months suggesting the distant effect of the treatment. The abscopal effect of radiation therapy was also observed by Okwan-Duodu and colleagues [41] in a case of patient with metastatic melanoma. In this case study, the patient underwent whole brain radiation therapy in combination with interleukin-2 immunotherapy. Following the treatment, the patient responded well and the metastatic disease was controlled indicating the abscopal effects of the therapy. Teulings and colleagues [42] reported that the radiation produced a systemic antimelanoma immune response in a melanoma patient with brain metastatic lesions. Two weeks after completing a course of whole brain radiation therapy (20 Gy, 5 fractions), the patient developed depigmentation within and outside of the target volume, at sites not previously irradiated suggesting an abscopal effect of radiation therapy.

Stamell and co-investigators [43] also observed an abscopal effect in a recurrent metastatic melanoma patient when treated with palliative radiation therapy in combination with ipilimumab. The combination therapy achieved a robust response in all untreated cutaneous metastases supporting the immune hypothesis for the abscopal effect of radiation therapy. Postow and colleagues [44] demonstrated a case of the abscopal effect of radiation therapy in a patient with metastatic melanoma who slowly progressed on ipilimumab maintenance treatment. Following treatment with palliative radiation therapy (28.5 Gy, 3 fractions), tumor regression was observed in both the irradiated tumor and non-irradiated metastases suggesting the abscopal effect of radiation therapy. The abscopal effects of radiation therapy were also reported by Hiniker et al. [45] in the case of a patient with recurrent stage IIA cutaneous melanoma. Radiation therapy in combination with ipilimumab not only produced a complete regression of the primary tumor but also achieved a complete resolution of all metastatic liver lesions suggesting the abscopal effect of radiation therapy. Kingsley [46] has also shown the abscopal effects of radiation therapy in a patient with inguinal, pelvic, and para-aortic lymphadenopathy from melanoma. Following irradiation of only the inguinal lymphatics with 14.4 Gy of fast neutrons in 12 fractions over 35 days, the patient experienced regression of all lymphadenopathy supporting the abscopal effects of the irradiation.

Abscopal effects of radiation therapy were also observed in other skin cancers such as sarcoma and Merkel cell carcinoma. Orton and co-investigators [47] reported the first case of a complete abscopal resolution of untreated lung metastases in a patient with a primary pleomorphic sarcoma of the head and neck treated with hypofractionated radiation therapy. Similarly, Cotter et al. [48] demonstrated the abscopal effect in a patient with metastatic Merkel cell carcinoma following irradiation. The localized radiation therapy not only controlled the tumor growth but also achieved complete resolution of all metastatic untreated lesions supporting the abscopal effect.

Abscopal effects in renal cell carcinoma

Abscopal effects of radiation therapy were reported sporadically in patients with renal cell carcinoma (RCC) using case studies (Table 3). In a most recent case series study, Giulio and colleagues [49] reported abscopal effect of radiation therapy in one of the three patients with metastatic RCC. After treatment with stereotactic body radiation therapy and subsequent treatment with anti-PD-1 inhibitor, with nivolumab, the patient experienced not only regression of the treated tumors but also achieved a distant response suggesting the abscopal effect. LaPlant and co-investigators [50] have shown that radiation therapy in combination with immune check point inhibitors exerted abscopal responses in RCC patient with innumerable pulmonary metastases. The patient remains disease-free without evidence of pulmonary or nodal metastases even 1 year after completing the combination therapy. Ishiyama et al. [51] have shown the spontaneous regression of thoracic metastases with the progression of brain metastases in a patient with metastatic RCC following SRS and SBRT to bone and spine lesions. Specifically, after irradiation, they reported a regression of the lung and lymph node metastases supporting the abscopal effects of radiation therapy.

Wersäll and colleagues [52] reported abscopal responses in 4 cases of 28 patients with metastatic RCC treated with the

Table 3 Summary of clinical case reports of abscopal effect of radiation therapy in kidney cancer

Patient		Primary treated? (yes/no)	Total radiation dose (Gy)	Radiation daily dose and fractions	Site with abscopal effect	Time to abscopal response	References
Gender	Age (years)						
Male	53	No, body radiation	25	5 Gy, 5 fractions	Non-irradiated lesions	NR	Giulio et al., 2018 [49]
Female	24	No, bone	27	9 Gy, 3 fractions	Non-irradiated lesions	7 months	LaPlant et al., 2017 [50]
Male	61	No, bone and spine	40	8 Gy, 5 fractions	Lung	1 month	Ishiyama et al., 2012 [51]
Male	69	No, lung metastases	30	15 Gy, 2 fractions	Untreated lung lesions	3 months	Wersäll et al., 2006 [52]
Female	83	Yes, kidney	32	8 Gy, 4 fractions	Lung lesions	2 years	Wersäll et al., 2006 [52]
Female	64	No, lung metastases	NR	NR	Untreated lung lesions	5 months	Wersäll et al., 2006 [52]
Female	55	No, kidney	32	8 Gy, 4 fractions	Lung metastasis	5 months	Wersäll et al., 2006 [52]
Male	58	Yes, kidney	20	2 Gy, 10 fractions	Pulmonary metastases	4 months	MacManus et al., 1994 [53]
Female	73	No, groin lesion	40	2.7 Gy, 15 fractions	Pulmonary lesion	2 months	Fairlamb et al., 1981 [54]
Male	53	No, bone lytic changes	21	1 Gy, 21 fractions	Stable disease	After radiation	Fairlamb et al., 1981 [54]

NR not reported

stereotactic radiation therapy (SRT). In 3 of the 4 patients, untreated metastatic disease completely regressed without a relapse at the time of reporting which ranged from 2 to 4 years post therapy. MacManus et al. [53] reported a representative case in which the patient had a large primary RCC with lung and mediastinal lymph node metastases that regressed after irradiation of the primary tumor. Fairlamb [54] also reported an abscopal effect in two patients with RCC. One of the two treated patients experienced a resolution in the pulmonary metastatic lesions and remained free of disease for over 4.0 years.

Abscopal effects in hepatocellular carcinoma

Although there are few case reports of abscopal effect in hepatocellular carcinoma (HCC), these cases primarily described regression of HCC itself due to radiation treatment delivered at a metastatic site (Table 4). Lock and colleagues [55] described a case of the abscopal effect in a patient with metastatic HCC. Following local radiation therapy to the liver, the patient had a treatment response in the liver and a complete response in the lung. Similarly, Okuma et al. [56] reported a case of the abscopal effect in a HCC patient who underwent an extended right hepatic lobectomy. The patient subsequently developed a single right lower lobe lung metastasis and a single mediastinal lymph node metastasis. The patient then underwent external beam radiation therapy which was delivered to the mediastinal lymph node. No other therapies were administered to the patient. Follow-up examination indicated not only a reduction in the lymph node size but also the spontaneous shrinking of the lung metastasis supporting the induction of an abscopal effect by the radiation therapy.

In another report, Nakanishi and colleagues [57] reported an abscopal effect of radiation therapy in a patient with HCC. In this case study, the patient had a selective transcatheter arterial embolization and localized external beam radiation therapy to the disease in the right lobe only. After 5 months, the patient's follow-up examination revealed the regression of bi-lobar disease. Nam and co-investigators [58] also described a case of abscopal regression of HCC and all bony metastatic sites following the completion of palliative radiation to a skull lesion. In this case, the patient initially refused any traditional therapy and instead started ingesting a mushroom called *Agaricus* (*Phellinus linteus*) for 18 months. However, the patient developed skull lesions. Then, the patient underwent palliative radiation therapy to a skull lesion. Follow-up at 3 months indicated a treatment response of the liver disease and regression of the untreated lesions indicating the abscopal effect of the radiation. In another case, Ohba et al. [59] reported an abscopal response in a patient with metastatic HCC. Two years after the initial liver-directed therapy, the patient was not responsive and developed vertebral bony metastasis. External beam radiation therapy was used as a palliative

Table 4 Summary of clinical case reports of abscopal effect of radiation therapy in liver cancer

Patient		Primary treated? (yes/no)	Total radiation dose (Gy)	Radiation daily dose and fractions	Site with abscopal effect	Time to abscopal response	References
Gender	Age (years)						
Male	71	Yes, liver	70	4.7 Gy, 15 fractions	Lung metastases	4 months	Lock et al., 2015 [55]
Male	63	Yes, liver	60.75	2.25 Gy, 27 fractions	Lung metastases	NR	Okuma et al., 2011 [56]
Male	79	No, inferior vena cava lesion	48	NR	Hepatic lesions	5 months	Nakanishi et al., 2008 [57]
Male	65	No, skull mass	30	NR	Metastatic lesions	10 months	Nam et al., 2005 [58]
Male	76	No, bone metastasis	36	NR	Hepatic lesions	10 months	Ohba et al., 1998 [59]

NR not reported

therapy to control the pain in the involved vertebra. The pain has reduced considerably and the patient's α-fetoprotein was found to be decreased. Imaging evaluation showed a resolution of the bony lesion and regression of the liver lesions to a very small size 10 months after the radiation treatment.

Abscopal effects in other solid tumors

The abscopal effect of radiation therapy was reported sporadically in cases of other malignant tumors such as colorectal, bladder, esophagus, breast, thyroid, pancreatic, thymoma, and other cancers (Table 5). Ebner and colleagues [60] reported the first two cases of an abscopal response following heavy-ion irradiation in patients with metastatic colorectal cancer. In this study, the two patients had an abscopal response after treatment with carbon ion irradiation. In one case, the patient experienced disease remission of 46 months with a reduction in the size of the non-irradiated tumor. In the second case, the patient had remission and stable disease of 92 months with a reduction in the size of the non-irradiated tumor. More specifically, abscopal responses were observed in the lymph nodes downstream of the treated site in both patients. Joe et al. [61] reported the first case of the abscopal effect of radiation therapy in squamous carcinoma of the anus with metastases to pelvic lymph nodes, liver, and bone. In this case, the patient had an abscopal response after treatment with palliative radiation therapy to the pelvis. Specifically, following treatment with palliative radiation therapy, the patient experienced a complete response not only in the primary anal tumor but also in bone and multiple liver metastases.

Smith and co-investigators [62] described an abscopal effect in a patient with pulmonary metastases from transitional cell carcinoma of the bladder. In this study, two cases of spontaneous complete regression of the lung metastases from the transitional cell carcinoma were reported. In one case, the regression of the metastatic lesions occurred after a course of radiation to the primary bladder cancer. In the second case, the lung lesions disappeared without treatment to the primary or metastatic cancers. Similarly, Lome and colleagues [63] reported a case of pulmonary metastases from transitional cell carcinoma of the bladder following treatment with radiation therapy. In this case study, the lung nodules disappeared after a course of radiation therapy to the urinary bladder suggesting its abscopal effect. Takaya et al. [64] reported a case of an abscopal regression in a patient who had an advanced uterine cervical carcinoma with para-aortic lymph node metastases. In this case, the patient was treated with external beam whole pelvis and intracavitary irradiation to the primary pelvic lesion. At follow-up, the patient was found to have not only a complete response of the primary pelvic lesion, but also the regression of her para-aortic lymph node metastases indicating an abscopal effect of radiation therapy.

Rees and Ross [65] described two cases of abscopal regression following radiation therapy in patients with metastatic esophageal cancer. Although the abscopal regression of the lung metastases from esophageal carcinoma was short lived after radiation therapy, in another patient, the abscopal response lasted approximately 20 months. In metastatic breast cancer, recently, Leung and colleagues [66] described the first case of the abscopal response following treatment with radiation therapy. In this case study, the patient with metastatic breast cancer received multiple fractions of high-dose radiation therapy that directly targeted the local breast tumor. An amelioration of distant bone metastasis was seen in the patient following radiation therapy indicating the abscopal response. Azami and co-investigators [67] reported on a case of the abscopal response in a patient with a metastatic breast cancer who received local radiation therapy. At presentation, the patient had a sizable breast mass and subsequent evaluation revealed metastatic osteolytic lesions in the left femur, lumbar vertebrae, and sacrum. The patient received localized palliative radiation therapy to a total dose of 60 Gy delivered in 30 fractions to the breast tumor. In addition, the patient received radiation therapy to some of her bone metastases. Follow-up evaluation after 10 months revealed a dramatic disease remission, determined as complete response, not only in all the irradiated sites but also in all the sites that were non-irradiated suggesting the abscopal response.

Table 5 Summary of clinical case reports of abscopal effect of radiation therapy in other solid tumors

Patient		Tumor type	Primary treated? (yes/no)	Total radiation dose (Gy)	Radiation daily dose and fractions	Site with abscopal effect	Time to abscopal response	References
Gender	Age (years)							
Male	75	Colorectal	Yes, left-sided mass	73.6	4.6 Gy, 16 fractions, 28 days (carbon ion RT)	Untreated tumor masses	1 month	Ebner et al., 2017 [60]
Male	85	Colorectal	No, aortic lymph node	50.4	4.2 Gy, 12 fractions, 21 days (carbon ion RT)	Untreated tumor	13 months	Ebner et al., 2017 [60]
Female	57	Anal	Yes, anal tumor	54	1.8 Gy, 30 fractions	Liver metastases	1 month	Joe et al., 2017 [61]
Male	78	Bladder	Yes, mid pelvis	70	NR	Pulmonary metastases	14 days	Smith et al., 1980 [62]
Male	66	Bladder	Yes, pelvis	40	NR, 28 days	Pulmonary lesions	5 months	Lome et al., 1970 [63]
Female	69	Uterine	Yes, pelvis	28.8	1.8 Gy, 16 fractions	Non-irradiated fields	NR	Takaya, et al., 2007 [64]
Male	49	Esophagus	No, lung lesions	40	2 Gy, 20 fractions	Non-irradiated lung lesions	After radiation	Rees et al., 1983 [65]
Male	56	Esophagus	Yes, lung	35	3.5 Gy, 10 fractions	Deltoid mass	After radiation	Rees et al., 1983 [65]
Female	65	Breast	Yes, local breast tumor	225	15 Gy, 15 fractions	Bone lesions	24 months	Leung et al., 2018 [66]
Female	64	Breast	Yes, local breast tumor	60	2Gy, 30 fractions	Non-irradiated local and distant lesions	10 months	Azami et al., 2018 [67]
Male	72	Thyroid	No, mediastinal lymph node	30	3 Gy, 10 fractions	Untreated lymph nodes	1 month	Tubin al., 2012 [68]
Male	54	Gastric	Yes, local gastric tumor	48	2 Gy, 24 fractions	Metastatic lesions	2 months	Sato et al., 2017 [69]
Female	67	Pancreatic	Yes, pancreatic tumor	45	3 Gy, 15 fractions	Metastatic lesions	1 month	Shi et al., 2017 [70]
Male	89	Thymoma	Yes, sternal mass	29.6	3.7 Gy, 8 fractions	Lung lesions	5 months	Lesueur et al., 2017 [71]
Male	87	Merkel cell carcinoma	Yes, local tumor	6	3 Gy, 2 fractions (neutron RT)	Non-irradiated Merkel cell carcinoma lesions	2 weeks	Schaub et al., 2018 [72]
Male	67	Mesothelioma	Yes, mediastinum and pleura	30	3 Gy, 10 fractions	Non-irradiated lesions	2 months	Barsky et al. 2019 [73]
Male	19	DGCT	No, right hilar metastasis	30	3 Gy, 10 fractions	Non-irradiated pulmonary metastases	2 weeks	Desar et al., 2016 [74]
Female	35	Papillary carcinoma	Yes, local tumor	40	2 Gy, 20 fractions	Mediastinal lesion	After radiation	Ehlers et al., 1973 [75]

DGCT diffuse type giant cell tumor, *NR* not reported, *RT* radiation therapy

Tubin and colleagues [68] described an abscopal response of radiation therapy in a patient with metastatic medullary thyroid carcinoma. These investigators, for the first time, observed the rare radiobiological phenomenon of the spontaneous regression of an un-irradiated tumor in a course of radiation of another, distant lesion in a patient affected by thyroid carcinoma. The abscopal effect of radiation therapy was also reported by Sato et al. [69] in the case of a patient with locally and peritoneally recurrent gastric cancer. In this case study, the patient experienced an abscopal response after treatment with intensity-modulated radiation therapy (IMRT) with concurrent adoptive T cell immunotherapy.

Shi and co-investigators [70] reported an abscopal response in a patient with advanced metastatic pancreatic cancer. Initially, the patient was administered single-agent chemotherapy gemcitabine. After the first cycle of gemcitabine therapy, the patient developed multiple metastases in the liver. The patient was then switched to another single-agent chemotherapy with paclitaxel. However, the patient's primary tumor progressed and an additional right pleura metastasis was developed. Later, the patient had failed targeted therapy with apatinib. The patient underwent palliative radiation therapy to a total dose of 45 Gy delivered in 15 fractions to her primary pancreatic tumor. Concurrently, the patient also had treatment with a granulocyte-macrophage colony-stimulating factor. Within weeks, the primary tumor on the pancreas shrunk significantly. Remarkably, the metastases had also shrunk significantly indicating the abscopal effect of radiation therapy.

Lesueur and co-investigators [71] reported on the occurrence of a post-radiation therapy abscopal response in a patient with a metastatic thymoma, which is the first case of the abscopal effect related to a thymic carcinoma reported in the literature. Following palliative radiation therapy to a sternal mass, the patient experienced not only a partial response of the primary tumor but also the complete regression of their lung lesions that were distant from the planned target volume without the use of antineoplastic agents or steroid therapy.

Schaub and colleagues [72] reported the first case of an abscopal effect in a patient with a recurrent Merkel cell carcinoma involving multiple skin and subcutaneous lesions on the face and scalp. The patient had a history of chronic lymphocytic leukemia. The patient was initially diagnosed with Merkel cell carcinoma of the glabellar region, for which he underwent a wide local excision with positive margins, and lymphovascular invasion. The patient then received conventionally fractionated radiation therapy delivered postoperatively to the primary surgical bed. The patient had an initial local response but progressed with an additional 3 dermal lesions. Despite treatment with immunotherapy using pembrolizumab, the patient's facial lesions continued to progress, and new dermal and subcutaneous lesions developed diffusely over his face and scalp. The patient received a short course of neutron radiation therapy (2×3 Gy) delivered to five of the most symptomatic lesions while continuing pembrolizumab. Two weeks following radiation therapy, a complete response was seen in all irradiated facial lesions. Remarkably, an additional four lesions located outside the radiation fields also completely regressed suggesting the abscopal effect of neutron radiation therapy.

Barsky and co-investigators [73] reported on the first-ever abscopal effect after palliative radiation therapy and immunotherapy in a patient with malignant pleural mesothelioma. Following his diagnosis, the patient initially received intrapleural interferon-alpha gene therapy but discontinued therapy due to the development of supraventricular tachycardia and superior vena cava syndrome due to the tumor burden. The patient emergently underwent palliative radiation therapy to a dose of 30 Gy delivered in 10 fractions to his mediastinum and pleura tumor followed by pemetrexed and cisplatin chemotherapy. Two months after radiation therapy, the patient experienced a dramatic treatment response within, as well as outside of, the irradiated field revealing the abscopal effect of neutron radiation therapy.

Desar et al. [74] described an abscopal response of radiation therapy in a patient with metastatic diffuse-type giant cell tumor. Following treatment with radiation therapy, the patient experienced not only the response in the right-sided irradiated hilar lesion but also a volumetric and metabolic response of the left-sided non-irradiated pulmonary metastases and an increase of uptake in one mediastinal lymph node suggesting an abscopal response from radiation therapy. It persisted for 6 months, after which he progressed and died from disease 3 months later. Ehlers and colleagues [75] reported the first case of an abscopal response in a patient with papillary adenocarcinoma. Following irradiation of the local tumor, these authors observed not only a local tumor response but also the regression of distant mediastinal lesions suggesting the abscopal effect of radiation therapy.

Conclusion and future perspectives

Radiation therapy has long been recognized as a potent local cytotoxic therapy for the management of malignant tumors. However, radiation therapy can also stimulate a systemic phenomenon which can lead to regression and annihilation of non-irradiated, distant tumor lesions. This regression of distant cancer metastases when the primary tumor irradiated is defined as the abscopal effect. The abscopal effects of radiation therapy have been documented since the beginning of the twentieth century and have made their way into sporadic clinical case reports.

Despite still being a rarely reported phenomenon, interest on the abscopal effects of radiation therapy is growing, particularly after the clinical development of novel immunotherapeutic agents for the treatment of cancers. Current evidence indicates that the abscopal effects of radiation therapy have been observed across all tumor types. Several recent studies have shown that radiation therapy exerts synergistic antitumor effects when combined with immunotherapy and produces a durable abscopal effect in a variety of advanced malignancies. Currently, several clinical trials are being conducted to address safety and other limitations of the combination of radiation therapy with novel immunotherapeutic agents. With parallel developments in radiation techniques and innovations in novel immunotherapeutic agents, there is a great motivation for cross-disciplinary research on combining these two modalities in cancer treatment. In addition, such efforts can boost the radiation-induced abscopal response rates and continue to improve the patients' chance of increased survival who benefit inadequately from radiation therapy or immunotherapy alone.

Compliance with ethical standards

This article is not a direct report of any investigation with the involvement of human or animal subjects performed by any of the authors.

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References

1. Jaffray DA (2012) Image-guided radiotherapy: from current concept to future perspectives. Nat Rev Clin Oncol 9(12):688–699
2. Orth M, Lauber K, Niyazi M, Friedl AA, Li M, Maihöfer C, Schüttrumpf L, Ernst A, Niemöller OM, Belka C (2014) Current concepts in clinical radiation oncology. Radiat Environ Biophys 53(1):1–29
3. Barton MB, Jacob S, Shafiq J, Wong K, Thompson SR, Hanna TP, Delaney GP (2014) Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. Radiother Oncol 112(1):140–144
4. Salama AK, Postow MA, Salama JK (2016) Irradiation and immunotherapy: from concept to the clinic. Cancer 122(11):1659–1671
5. Mole RH (1953) Whole body irradiation; radiobiology or medicine? Br J Radiol 26(305):234–241
6. Kaminski JM, Shinohara E, Summers JB, Niermann KJ, Morimoto A, Brousal J (2005) The controversial abscopal effect. Cancer Treat Rev 31(3):159–172
7. Jatoi I, Benson JR, Kunkler I (2018) Hypothesis: can the abscopal effect explain the impact of adjuvant radiotherapy on breast cancer mortality? NPJ Breast Cancer 4:8
8. Rontgen WC (1896) On a new kind of rays. Science 3:227–231
9. Becquerel AH (1896) Sur les radiations ´emises par phosphorescence. Rend Acad Sci 122:420–421
10. Curie P, Curie M (1898) Sur une substance nouvelle radioactive, contenue dans la pechblende. C R Acad Sci 127:125
11. Schäfer W, Witte E (1932) Über eine neue Körperhöhlenröntgenröhre zur Bestrahulung von Uterustumoren. Strahlentherapie 44:283
12. Becquerel AH, Curie P (1901) Action physiologique des rayons de radium. C R Acad Sci 132:1289–1291
13. Coolidge WD (1913) A powerful Rontgen ray tube with a pure electron discharge. Phys Rev 2:409–413
14. Grubbe EH (1933) Priority in the therapeutic use of X-rays. Radiology. 21:156–162
15. Thoraeus RA (1932) A study of ionization method for measuring the intensity and absorption of roentgen rays and of the efficiency of different filters used in therapy. Acta Radiol 18:1–86
16. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gerard JP (2013) Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol 10(1):52–60
17. Slater JM (2012) From X-rays to ion beams: a short history of radiation therapy. In: Linz U (ed) Ion beam therapy, biological and medical physics, biomedical engineering. Springer-Verlag, Berlin, pp 3–16
18. Gianfaldoni S, Gianfaldoni R, Wollina U, Lotti J, Tchernev G, Lotti T (2017) An overview on radiotherapy: from its history to its current applications in dermatology. Open Access Maced J Med Sci 5(4):521–525
19. Ross GM (1999) Induction of cell death by radiotherapy. Endocr Relat Cancer 6(1):41–44
20. Vatner RE, Cooper BT, Vanpouille-Box C, Demaria S, Formenti SC (2014) Combinations of immunotherapy and radiation in cancer therapy. Front Oncol 4:325
21. Kamrava M, Bernstein MB, Camphausen K, Hodge JW (2009) Combining radiation, immunotherapy, and antiangiogenesis agents in the management of cancer: the Three Musketeers or just another quixotic combination? Mol BioSyst 5(11):1262–1270
22. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, Benci JL, Xu B, Dada H, Odorizzi PM, Herati RS, Mansfield KD, Patsch D, Amaravadi RK, Schuchter LM, Ishwaran H, Mick R, Pryma DA, Xu X, Feldman MD, Gangadhar TC, Hahn SM, Wherry EJ, Vonderheide RH, Minn AJ (2015) Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 520(7547): 373–377
23. Hodge JW, Guha C, Neefjes J, Gulley JL (2008) Synergizing radiation therapy and immunotherapy for curing incurable cancers. Opportunities and challenges. Oncology (Williston Park) 22(9): 1064–1070 discussion 1075, 1080-1061, 1084
24. Bitran J (2019) The abscopal effect exists in non-small cell lung cancer: a case report and review of the literature. Cureus. 11(2): e4118
25. Kim JO, Kim CA (2019) Abscopal resolution of a hepatic metastasis in a patient with metastatic cholangiocarcinoma following radical stereotactic body radiotherapy to a synchronous early stage non-small cell lung cancer. Cureus. 11(2):e4082
26. Lin X, Lu T, Xie Z, Qin Y, Liu M, Xie X, Li S, Zhou C (2019) Extracranial abscopal effect induced by combining immunotherapy with brain radiotherapy in a patient with lung adenocarcinoma: a case report and literature review. Thorac Cancer 10(5):1272–1275
27. Hamilton AJ, Seid J, Verdecchia K, Chuba P (2018) Abscopal effect after radiosurgery for solitary brain metastasis from non-small cell lung cancer. Cureus. 10(12):e3777
28. Britschgi C, Riesterer O, Burger IA, Guckenberger M, Curioni-Fontecedro A (2018) Report of an abscopal effect induced by stereotactic body radiotherapy and nivolumab in a patient with metastatic non-small cell lung cancer. Radiat Oncol 13(1):102
29. Cong Y, Shen G, Wu S, Hao R (2017) Abscopal regression following SABR for non-small-cell-lung cancer: a case report. Cancer Biol Ther. 18(1):1–3
30. Katayama K, Tamiya A, Koba T, Fukuda S, Atagi S (2017) An abscopal response to radiation therapy in a patient with metastatic

non-small cell lung cancer: a case report. J Cancer Sci Ther 9:365–367
31. Cummings AL, Kaprealian TB, Sarantopoulos AP, Mendenhall MA, Goldman JW An abscopal effect in a case of neuroendocrine atypical carcinoid lung cancer. Appl Radiation Oncol 2017:39–39
32. Komatsu T, Nakamura K, Kawase A (2017) Abscopal effect of nivolumab in a patient with primary lung cancer. J Thorac Oncol 12(9):e143–e144
33. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC (2013) An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res 1(6):365–372
34. Siva S, Callahan J, MacManus MP, Martin O, Hicks RJ, Ball DL (2013) Abscopal [corrected] effects after conventional and stereotactic lung irradiation of non-small-cell lung cancer. J Thorac Oncol 8(8):e71–e72
35. Yoon SM, Lee JS (2012) Case of abscopal effect with metastatic non-small-cell lung cancer. Oncothermia J 5:53–57
36. Tsui JM, Mihalcioiu C, Cury FL (2018) Abscopal effect in a stage IV melanoma patient who progressed on pembrolizumab. Cureus. 10(2):e2238
37. Sims-Mourtada J, Sims-Mourtada S, Casteneda S et al (2018) Dosimetric characterization of an abscopal response in a patient with oligometastatic melanoma undergoing concurrent treatment with pembrolizumab and stereotactic body radiotherapy. Cancer Stud Mol Med 4:1–4
38. Komori T, Otsuka A, Irie H, Horiguchi A, Honda T, Kabashima K (2018) Drastic effect on giant lung metastatic melanoma by sequential administration of nivolumab with ipilimumab/radiation combination therapy. J Dermatol 45(1):e7–e8
39. Sperduto W, King DM, Watanabe Y, Lou E, Sperduto PW (2017) Case report of extended survival and quality of life in a melanoma patient with multiple brain metastases and review of literature. Cureus. 9(12):e1947
40. Fujimura T, Kambayashi Y, Furudate S, Hidaka T, Sato Y, Tanita K, Tono H, Tsukada A, Hashimoto A, Aiba S (2017) Successful treatment of multiple in-transit melanomas on the leg with intensity-modulated radiotherapy and immune checkpoint inhibitors: report of two cases. J Dermatol 44(5):592–595
41. Okwan-Duodu D, Pollack BP, Lawson D, Khan MK (2015) Role of radiation therapy as immune activator in the era of modern immunotherapy for metastatic malignant melanoma. Am J Clin Oncol 38(1):119–125
42. Teulings HE, Tjin EP, Willemsen KJ et al (2013) 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 168(4):733–738
43. Stamell EF, Wolchok JD, Gnjatic S, Lee NY, Brownell I (2013) The abscopal effect associated with a systemic anti-melanoma immune response. Int J Radiat Oncol Biol Phys 85(2):293–295
44. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, Mu Z, Rasalan T, Adamow M, Ritter E, Sedrak C, Jungbluth AA, Chua R, Yang AS, Roman RA, Rosner S, Benson B, Allison JP, Lesokhin AM, Gnjatic S, Wolchok JD (2012) Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med 366(10):925–931
45. Hiniker SM, Chen DS, Reddy S, Chang DT, Jones JC, Mollick JA, Swetter SM, Knox SJ (2012) A systemic complete response of metastatic melanoma to local radiation and immunotherapy. Transl Oncol 5(6):404–407
46. Kingsley DP (1975) An interesting case of possible abscopal effect in malignant melanoma. Br J Radiol 48(574):863–866
47. Orton A, Wright J, Buchmann L, Randall L, Hitchcock YJ (2016) A case of complete abscopal response in high-grade pleiomorphic sarcoma treated with radiotherapy alone. Cureus. 8(10):e821
48. Cotter SE, Dunn GP, Collins KM, Sahni D, Zukotynski KA, Hansen JL, O'Farrell DA, Ng AK, Devlin PM, Wang LC (2011) Abscopal effect in a patient with metastatic Merkel cell carcinoma following radiation therapy: potential role of induced antitumor immunity. Arch Dermatol 147(7):870–872
49. Giulio F, Donato P, Beatrice D et al (2018) A case report series of renal cell carcinoma patients treated with Nivolumab and radiotherapy. J Oncol Res Ther. https://doi.org/10.29011/22574-29710X.000050
50. LaPlant Q, Deselm C, Lockney NA, Hsieh J, Yamada Y (2017) Potential abscopal response to dual checkpoint blockade in RCC after reirradiation using dose-painting SBRT. Pract Radiat Oncol 7(6):396–399
51. Ishiyama H, Teh BS, Ren H, Chiang S, Tann A, Blanco AI, Paulino AC, Amato R (2012) Spontaneous regression of thoracic metastases while progression of brain metastases after stereotactic radiosurgery and stereotactic body radiotherapy for metastatic renal cell carcinoma: abscopal effect prevented by the blood-brain barrier? Clin Genitourin Cancer 10(3):196–198
52. Wersall PJ, Blomgren H, Pisa P, Lax I, Kalkner KM, Svedman C (2006) Regression of non-irradiated metastases after extracranial stereotactic radiotherapy in metastatic renal cell carcinoma. Acta Oncol 45(4):493–497
53. MacManus MP, Harte RJ, Stranex S (1994) Spontaneous regression of metastatic renal cell carcinoma following palliative irradiation of the primary tumour. Ir J Med Sci 163(10):461–463
54. Fairlamb DJ (1981) Spontaneous regression of metastases of renal cancer: a report of two cases including the first recorded regression following irradiation of a dominant metastasis and review of the world literature. Cancer. 47(8):2102–2106
55. Lock M, Muinuddin A, Kocha WI, Dinniwell R, Rodrigues G, D'Souza D (2015) Abscopal effects: case report and emerging opportunities. Cureus. 7(10):e344
56. Okuma K, Yamashita H, Niibe Y, Hayakawa K, Nakagawa K (2011) Abscopal effect of radiation on lung metastases of hepatocellular carcinoma: a case report. J Med Case Rep 5:111
57. Nakanishi M, Chuma M, Hige S, Asaka M (2008) Abscopal effect on hepatocellular carcinoma. Am J Gastroenterol 103(5):1320–1321
58. Nam SW, Han JY, Kim JI et al (2005) Spontaneous regression of a large hepatocellular carcinoma with skull metastasis. J Gastroenterol Hepatol 20(3):488–492
59. Ohba K, Omagari K, Nakamura T, Ikuno N, Saeki S, Matsuo I, Kinoshita H, Masuda J, Hazama H, Sakamoto I, Kohno S (1998) Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. Gut. 43(4):575–577
60. Ebner DK, Kamada T, Yamada S (2017) Abscopal effect in recurrent colorectal cancer treated with carbon-ion radiation therapy: 2 case reports. Adv Radiat Oncol 2(3):333–338
61. Joe MB, Lum JJ, Watson PH, Tonseth RP, McGhie JP, Truong PT (2017) Radiation generates an abscopal response and complete resolution of metastatic squamous cell carcinoma of the anal canal: a case report. J Gastrointest Oncol 8(6):E84–E89
62. Smith JA Jr, Herr HW (1980) Spontaneous regression of pulmonary metastases from transitional cell carcinoma. Cancer. 46(6):1499–1502
63. Lome LG, Navani S, Aral IM (1970) Spontaneous regression of pulmonary metastases from transitional cell carcinoma of the bladder. Cancer. 26(2):415–418
64. Takaya M, Niibe Y, Tsunoda S, Jobo T, Imai M, Kotani S, Unno N, Hayakawa K (2007) Abscopal effect of radiation on toruliform para-aortic lymph node metastases of advanced uterine cervical carcinoma–a case report. Anticancer Res 27(1B):499–503
65. Rees GJ, Ross CM (1983) Abscopal regression following radiotherapy for adenocarcinoma. Br J Radiol 56(661):63–66

66. Leung HW, Wang SY, Jin-Jhih H, Chan AL (2018) Abscopal effect of radiation on bone metastases of breast cancer: a case report. Cancer Biol Ther. 19(1):20–24
67. Azami A, Suzuki N, Azami Y, Seto I, Sato A, Takano Y, Abe T, Teranishi Y, Tachibana K, Ohtake T (2018) Abscopal effect following radiation monotherapy in breast cancer: a case report. Mol Clin Oncol 9(3):283–286
68. Tubin S, Casamassima F, Menichelli C, Pastore G, Fanelli M, Crisci R (2012) A case report on metastatic thyroid carcinoma: radiation-induced bystander or abscopal effect? J Cancer Sci Ther. 4:408–411
69. Sato H, Suzuki Y, Yoshimoto Y, Noda SE, Murata K, Takakusagi Y, Okazaki A, Sekihara T, Nakano T (2017) An abscopal effect in a case of concomitant treatment of locally and peritoneally recurrent gastric cancer using adoptive T-cell immunotherapy and radiotherapy. Clin Case Rep 5(4):380–384
70. Shi F, Wang X, Teng F, Kong L, Yu J (2017) Abscopal effect of metastatic pancreatic cancer after local radiotherapy and granulocyte-macrophage colony-stimulating factor therapy. Cancer Biol Ther 18(3):137–141
71. Lesueur P, Chevalier F, Stefan D, Habrand JL, Lerouge D, Gervais R (2017) Review of the mechanisms involved in the abscopal effect and future directions with a focus on thymic carcinoma. Tumori. 103(3):217–222
72. Schaub S, Stewart R, Sandison G et al (2018) Does neutron radiation therapy potentiate an immune response to Merkel cell carcinoma? Int J Particle Ther 5:183–195
73. Barsky AR, Cengel KA, Katz SI, Sterman DH, Simone CB (2019) First-ever abscopal effect after palliative radiotherapy and Immunogene therapy for malignant pleural mesothelioma. Cureus. 11(2):e4102
74. Desar IM, Braam PM, Kaal SE, Gerritsen WR, Oyen WJ, van der Graaf WT (2016) Abscopal effect of radiotherapy in a patient with metastatic diffuse-type giant cell tumor. Acta Oncol 55(12):1510–1512
75. Ehlers G, Fridman M (1973) Abscopal effect of radiation in papillary adenocarcinoma. Br J Radiol 46(543):220–222
76. Golden EB, Chhabra A, Chachoua A, Adams S, Donach M, Fenton-Kerimian M, Friedman K, Ponzo F, Babb JS, Goldberg J, Demaria S, Formenti SC (2015) Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. Lancet Oncol 16(7):795–803
77. Hiniker SM, Reddy SA, Maecker HT, Subrahmanyam PB, Rosenberg-Hasson Y, Swetter SM, Saha S, Shura L, Knox SJ (2016) A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma. Int J Radiat Oncol Biol Phys 96(3):578–588

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