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A review of radiation induced abscopal effect: combining radiotherapy and immunotherapy to treat the untreated distant metastatic tumours

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Literature Review

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Abstract

Background: Radiotherapy is an effective and significant mode of definitive cancer treatment with well-established local tumour control success, especially in the treatment of localised tumours. Although, for metastatic disease, the role of radiotherapy has generally been limited to palliation of symptoms. In the treatment of metastatic diseases settings, the radiation therapy technique has always been confronted with the challenge of the simultaneous treatment of all of the various distant metastatic tumour sites, however, some recent evidence suggests that radiotherapy can potentially induce anticancer immune responses whose effectors potentially migrate to distant metastatic tumours to provoke their regression in cancer patients. Thus, unirradiated distant metastatic tumour sites can exhibit a delayed therapeutic response termed the abscopal effect.

Materials and methods: This paper reports on a review of the abscopal effect, including its biological mechanism, the effect of radiation dose and fractionation regime and the timing of immunotherapy administration on radiotherapy-induced abscopal effect, the enhancement of radiotherapy-induced abscopal effects with immunotherapy, the effect of the location of the irradiated tumour and the radiotherapy of multiple tumour sites on the likelihood and effectiveness of inducing abscopal responses in the preclinical and clinical settings and also reports on some evidence of clinical observations in patients.

Conclusions: Although abscopal effects of radiotherapy are still relatively rare in patients, it has gained a lot of interest due to recent development and use of immunotherapy strategies incorporating combinations of targeted immunomodulators and immune checkpoint blockade with radiation therapy. The enhancement of cancer immunotherapy could potentially enable the translation of the concept of abscopal effect into the clinics as a new strategy to induce therapeutically effective anti-tumour immune responses in cancer patients. The combination of radiotherapy and immunotherapy has the potential to expand the role of radiotherapy from a purely local tumour control treatment to play a significant role in advanced and metastatic tumour control and this could likely lead to a paradigm shift in the treatment of patients with metastatic cancer.

Introduction

Radiation therapy is an effective and a significant mode of definitive cancer treatment with the well-established success of local tumour control, especially in the treatment of localised tumours, and the utilisation rate (percentage of cancer patients who received radiotherapy as part of their treatment during their illness) has been increasing steadily with a global goal of reaching about 50% in most developed countries.[1,2] Although, for distant metastatic diseases, the role of radiotherapy has generally been limited to palliation of symptoms.[1,3–5] According to Yilmaz et al.,[5] the radiobiology of radiotherapy hypothesised that the cytotoxic effects of radiation result from direct damage to the deoxyribonucleic acid (DNA) and an indirect generation of cell-damaging free radicals, thus making this treatment modality a local therapy characterised by a high degree of spatial accuracy. However, other investigations[6–15] have demonstrated that radiotherapy can also induce localised bystander effects, whereby neighbouring unirradiated cells exhibit irradiated effects as a result of signals received from nearby irradiated cells. In the treatment of metastatic diseases settings, a radiation therapy technique has always been confronted with the challenge of the simultaneous treatment of all of the various distant metastatic tumour sites; however, recent evidence suggests that radiotherapy can potentially induce anticancer immune responses whose effectors, most likely T-lymphocytes, could potentially migrate to distant metastatic tumours to provoke regression in cancer patients.[11–15]

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According to Kroemer and Zitvogel,[11] local radiotherapy exerts cytotoxic effects on locally irradiated tumours and could also potentially lead to delayed regression of distant metastatic unirradiated tumours, an effect which is therapeutic and mediated by the immune system. Thus, distant metastatic tumours, which have not been irradiated, can exhibit delayed therapeutic response and these effects have been documented for several cancers including lymphoma, adenocarcinoma, melanoma, lung cancer, breast cancer, sarcomas, hepatocellular carcinoma or Merkel cell carcinoma and the clinical observations consistent with this effect is termed the abscopal effect.[10,11,16–20] Golden et al.[21] reported that a combination of radiation therapy with granulocyte-macrophage colony-stimulating factor can induce objective abscopal responses in patients with metastatic solid tumours, suggesting a promising technique to establish an *in situ* anti-tumour vaccine. Other studies have also reported that the combination of radiotherapy and immunotherapy has the potential to immunise patients against tumour, acting as an anti-tumour vaccine and could lead to the regression of both the directly irradiated tumour and the distant metastatic unirradiated tumours.[14,22–26] Therefore, the purpose of this paper is to report on a literature review of the abscopal effect, including its biological mechanism, the effect of different radiation dose and fractionation regime and the timing of immunotherapy on radiotherapy-induced abscopal effect, the enhancement of radiotherapy-induced abscopal effects with immunotherapy, the effect of the location of the irradiated tumour and the radiotherapy of multiple tumour sites on the likelihood and effectiveness of inducing abscopal responses in the preclinical and clinical settings and also to report on some evidence of clinical observations in patients.

The Abscopal Effect

The abscopal effect is a very rare anti-tumour immune response to radiation therapy that has been observed in patients with various types of metastatic cancers receiving palliative radiotherapy to a single metastatic site. It refers to the effect whereby radiotherapy delivered at one tumour site may lead to regression of metastatic tumours at distant sites that are outside of the field of radiation (i.e., not directly irradiated), implying an indirect anti-tumour effect induced by local radiotherapy.[11–15,27,28] The abscopal (from ab-, a prefix meaning 'away from' and scopus (Latin) meaning 'a target') effect was first described by Mole in 1953 and since then several investigations have been ongoing to test the ability of local radiotherapy to induce an *in situ* tumour vaccine and techniques to enhance the systemic responses to immune checkpoint inhibitors in cancer patients or to investigate the combination of radiation with different immune modulators to enhance the abscopal response in patients.[5,16,26,29] According to Shi et al.,[26] some preconditions may be required to induce the abscopal response, including the use of precision radiotherapy to ensure the protection of surrounding normal tissues and adjacent draining lymph nodes (which participate ineffective immune responses), a richly vascularised targeted tumour region [since the radiation-induced increase in vascular permeability can promote extravasation of effector cluster of differentiation 8 positive (CD8+) T-cells at the tumour site] and high concentrations of CD8+ T-cells (which are needed to kill tumour cells). Furthermore, Shi et al.[26] reported that the abscopal effect can be enhanced by the induction of interferon-γ (IFN-γ) producing cytotoxic T-cells or could be abolished by the depletion of CD4+ (also known as T helper cells) or CD8+ T-cells. According to Azami et al.,[16] the abscopal effect has become relevant and clinically meaningful in cancer patients due to the recent development and use of immunotherapy strategies incorporating combinations of targeted immunomodulators and immune checkpoint blockade with radiation therapy.

The Biological Mechanism of the Abscopal Effect

Although the biological mechanism underlying the abscopal effect is still not very clear, several investigations[5–30] have been ongoing to understand the biological rationale behind the effect and have recently gained more interest as a result of the successes achieved with the combination of immunotherapy and radiotherapy for cancer patients. Demaria and Formenti[14] reported that both preclinical and clinical evidence shows that multiple factors regulate the radiation interaction with the immune system both within and outside of the irradiated tumour volume. According to Yilmaz et al.,[5] radiotherapy exerts direct cytotoxic effects on tumour cells, re-programmes the tumour microenvironment to exert a potent anti-tumour immune response, enhances anti-tumour immunity and initiates immunogenic cell death causing the production and release of cytokines and chemokines into the tumour microenvironment. These effects can then lead to chemoattraction and infiltration of dendritic cells to the tumour site and the activation of these dendritic cells [essential antigen-presenting cells (APC)] and up-regulation of cytotoxic T-lymphocytes are responsible for the abscopal effect mechanism. Others[12,14,26,29] have also reported that the abscopal effect is most likely mediated by the immune system and induces an immunogenic tumour cell death (a process which involves dendritic cells, T regulatory cells, and suppressor cells as critical mediators) and alters the tumour microenvironment to enhance recruitment of anti-tumours T-cells. According to Dewan et al.,[12] these concepts support the hypothesis that radiation can enhance both the priming and the effector phase of the anti-tumour immune response. Suek et al.[15] and Trommer et al.[29] have expressed that the occurrence of an abscopal response is led by an anti-tumour immune response that is activated by the release of cell fragments, neoantigens, cellular damage-associated molecular patterns (DAMP) and cytokines. Shi et al.[26] also reported that in the tumour microenvironment, radiation-induced tumour cell death and the specific antigens that are released lead to dendritic cells activation that can travel to regional lymph nodes, where they initiate and enhance anti-tumours responses of effector T-cells through presenting specific antigens to the metastatic tumours.

Radiation Therapy and the Abscopal Effects

Several studies[9,12,29–34] are ongoing to determine the factors that impact the optimal use of radiation to induce an *in situ* anti-tumour vaccine at the irradiated tumour site to achieve abscopal responses. These studies include the effect of the radiation dose and fractionation, schedule and technique of radiation delivery, the sequencing with different immune modulators and the susceptibility of different tumour types and carriers, or whether the location of the tumour that is irradiated or whether irradiating multiple tumour sites influences the likelihood and effectiveness of inducing abscopal responses in patients. According to Trommer et al.,[29] the probability of occurrence of the abscopal response with radiotherapy can be enhanced by modulating the tumour microenvironment which could be achieved by modifying the radiation dose, fractionation, the site of irradiation and timing, or by combined radiotherapy with systemic therapies. Tubin et al.[31] reported on radiation-induced abscopal effect on five oligometastatic patients

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treated with high-dose radiotherapy. Three patients had large hypoxic tumours in the lung, one patient had the tumour in the neck and the last patient had the tumour in the mediastinum. All the tumours were partially irradiated by targeting the central hypoxic region which corresponded to about 30% of total gross tumour volume and they observed significant abscopal response in the unirradiated tumours. They reported that by considering the clinical benefit:toxicity ratio, the clinical utilisation of the biological properties of the abscopal response induced by partial irradiation of large tumour masses could make the abscopal effect more effective for the treatment of advanced metastatic cancers and an ideal treatment option for symptomatic patients. They concluded that by inducing distal responses, radiation-induced abscopal effects in the hypoxic volume of tumours may potentially offer one more possibility for a cure for oligometastatic patients.[31]

Effect of Radiation Dose and Fractionation Regime on Abscopal Response

Recent studies[9,12,30,32,35–40] have reported that the potential efficacy of radiation to induce an abscopal response in cancer patients is impacted by the radiotherapy regime; that is whether radiotherapy is delivered as a single-dose or fractionated. Although, according to Buchwald et al.[30] and Zhang and Niedermann,[35] the effectiveness of the abscopal response is similar for different hypofractionated regimens with similar biological equivalent dose. Dewan et al.[12] investigated the hypothesis that the type of dose fractionation regimen determines the ability of radiotherapy to synergise with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody using TSA mouse breast carcinoma and MCA38 mouse colon carcinoma models. The mice injected with these cell lines were assigned to groups receiving no radiotherapy or to three distinct regimens of mice receiving radiotherapy at 20 Gy in one fraction, 8 Gy in three fractions or 6 Gy in five fractions in combination with or without 9H10 monoclonal antibody against CTLA-4. They reported that the single-dose radiotherapy regimens caused growth delay of the primary tumours but had no effect on the secondary tumours outside the irradiated field. However, fractionated radiotherapy combined with 9H10 significantly inhibited the growth of the secondary tumours outside the irradiated field and the frequency of CD8+ T-cells (which shows tumour-specific IFN-γ production) was proportional to the inhibition of the secondary tumour. They concluded that fractionated but not single-dose radiotherapy induces abscopal response when combined with anti-CTLA-4 antibody. Habets et al.[9] assessed whether humoral anti-tumour response with fractionated radiotherapy in murine 67NR mammary carcinoma animal cell lines exhibits an abscopal tumour growth delay. The mice were injected with 67NR tumour cell lines at the right flank (to simulate the primary tumour) and at the left flank (to simulate the secondary tumour) and were separated into four groups of untreated, treated with FMS-like tyrosine kinase 3 ligand (FLT3L) only, radiotherapy only and radiotherapy plus FLT3L. Radiation therapy was delivered at a dose of 8 Gy in three fractions to the primary tumour only. They observed a delay in both the primary and secondary tumour growth within mice treated with radiotherapy and radiotherapy plus FLT3L and concluded that fractionated radiotherapy with or without the administration of FLT3L induces abscopal effects in the 67NR mouse model.[9] Wu et al.[32] examined the control of metastatic castration-resistant prostate cancer mediated by the radiotherapy-induced abscopal response in mice treated with androgen deprivation therapy (ADT). They injected androgen-sensitive prostate cancer cell lines (human LNCaP) to the right thigh (to simulate the primary tumour) and upper left back (to simulate the secondary tumour) in the same nude mice. Radiation therapy was delivered to the primary tumour to a dose of 8 Gy in three fractions over 1 week and they observed that hypofractionated radiotherapy has the potential to alter the immunosuppressive tumour environment and induce an immune-mediated abscopal response. Furthermore, they observed a decreased antigen Ki-67 in the secondary unirradiated tumours of mice treated with radiotherapy and ADT and reported that radiotherapy to the primary tumour was associated with elevated numbers of tumour-infiltrating lymphocytes (TILs) in the secondary unirradiated tumours of mice treated with ADT. Moreover, inhibiting interleukin 6 (IL-6) enhanced the radiotherapy-induced tumouricidal effect in irradiated tumours and induced greater regression of unirradiated tumours in the mice treated with ADT. They concluded that high-dose local radiotherapy may increase the response to ADT in unirradiated tumours by increasing anti-tumour immunity and that IL-6 inhibition increases the anti-tumour immune response and potentially augment the abscopal response induced by high-dose local radiotherapy.[32]

Morisada et al.[36] investigated immune correlates, primarily treated tumour and distant untreated tumour control rates in a syngeneic mouse model of head and neck squamous cell carcinoma using high-dose hypofractionated radiotherapy delivered at 8 Gy in two fractions or low-dose daily fractionated delivery at 2 Gy in ten fractions in combination with concurrent programmed death 1 (PD-1) monoclonal antibody (PD-1 mAb). They reported that high-dose hypofractionated radiotherapy preserved peripheral and tumour-infiltrating CD8+ T-lymphocyte accumulation and activation, reduced peripheral and granulocytic myeloid-derived suppressor cell (gMDSC) accumulation and did not altered regulatory T-lymphocytes. Furthermore, the expression of interferon (IFN)-responsive gene MHC class I and PD-L1 and type-I IFN (IFNβ) and type-II IFN (IFNγ) levels was higher in tumours treated with hypofractionated radiotherapy and the addition of PD-1 mAb reversed adaptive immune resistance and resulted in enhancement of CD8+ cell-dependent control of both primary and distant tumours. They concluded that high-dose hypofractionated radiotherapy preserves or enhances anti-tumour immunity and when combined with PD-1 mAb to reverse adaptive immune resistance, promotes anti-tumour immunity to control primary and distant tumours.[36] Zhang and Niedermann[35] compared three different hypo-fractionated radiotherapy schedules with equivalent total biological effective dose in combination with the administration of an anti-PD-1 checkpoint blocking antibody in metastatic melanoma and breast cancer mouse models. Tumour cells were injected subcutaneously into the right flank (to simulate the primary tumour) and left flank (to simulate the secondary tumour) of the mice and the primary tumours were treated with 9·18 Gy in three fractions or 6·43 Gy in five fractions in combination with anti-PD-1 antibody administration. They observed growth inhibition of both the irradiated primary and the unirradiated secondary tumours and overall survival were similar with all hypofractionated/anti-PD-1 combinations for both models and was strongly dependent on CD8+ T-cells. Furthermore, TIL infiltration and local and systemic tumour-specific CD8+ T-cell responses were also similar, irrespective of using a short or extended hypofractionated regime. They concluded that a combined hypofractionated/PD-1 therapy extending into the period during which treatment-induced T-cells infiltrate the irradiated

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tumour can provoke local and systemic anti-tumour effects if lymph nodes supply sufficient tumour-specific T-cells.[35]

Effect of the location of the irradiated tumour on abscopal response

According to Poleszczuk et al.[33] and Tang et al.,[41] the location of the tumour that is irradiated or treated may potentially impact the likelihood of inducing abscopal responses in patients. Poleszczuk et al.[33] used a statistical model to investigate if the location of an irradiated tumour increases the probability of observing an abscopal effect. In the model, they hypothesised that an abscopal effect can only be attained if there are moderate amounts of activated T-cells at the primary tumour site reaching the secondary metastatic sites. They also assumed that the movement of the activated T-cells from the irradiated tumour site to the metastatic site is determined by the physiological blood flow to the metastatic site and by the initial imprinting of the T-cells by the tumour antigen-presenting dendritic cells. They were able to demonstrate the potential of using a statistical model to identify patient-specific treatment targets with the highest probability of inducing abscopal effects. Tang et al.[41] conducted a phase I clinical trial to evaluate the abscopal effects with tumours located in the lung and liver using the stereotactic ablative radiotherapy (SABR) technique in combination with ipilimumab. The patients received the SABR either concurrently or sequentially with ipilimumab and were stratified into patients receiving SABR at 50 Gy in four fractions to the liver or lung concurrently with ipilimumab; SABR at 50 Gy in four fractions to the liver or lung sequentially with ipilimumab; SABR at 60 Gy in ten fractions to the lung or liver sequential sequentially with ipilimumab. They observed that clinical benefit was associated with elevated peripheral CD8+ T-cells, CD8+/CD4+ T-cell ratio, and proportion of CD8+ T-cells expressing 4-1BB and PD-1 and that the liver irradiation produced greater T-cell activation. They concluded that high-dose SABR and ipilimumab is tolerable and has promising clinical benefit outside the irradiated field, peripheral T-cell markers may predict clinical benefit and that the liver irradiation is associated with greater systemic immune activation than the lung irradiation demonstrating that the location of the irradiated tumour (lung versus liver) is important for eliciting an immune response.

Effect of irradiating multiple metastatic tumour sites on abscopal response

The current concept of the abscopal effect has been based primarily on the radiotherapy of a single primary or metastatic tumour in combination with immunotherapy to enable the regression of tumours at anatomical locations outside the irradiation field due to local activation of systemic anti-tumour immunity. However, Brooks et al.[42] have recently proposed that to optimise the effectiveness of radiotherapy-induced abscopal effects with immune-checkpoint inhibition, radiotherapy will be required to be delivered to as much of the tumour burdens as can be safely irradiated, instead of the irradiation of a single tumour site. Tang et al.[41] have reported that a successful anti-tumour immune response will most likely be limited to lesions that share similar characteristics of the single irradiated lesion and the likelihood of a successful immunogenic event is also influenced by the tumour microenvironment, the surrounding tissue or organ, and the nodal characteristics of the irradiated tumour. Therefore, Brooks et al.[42] expressed that the consideration of these factors is necessary when considering optimising the use of radiotherapy with immune-checkpoint inhibition for an effective abscopal response. Furthermore, they suggested that a successful enhancement of the effects of immune-checkpoint inhibition requires the recognition of and priming of the immune system to given tumour-associated antigens (TAAs) and these TAAs must also be shared by the distant tumours. However, Heppner and Shekhar[43] reported that the heterogeneity of most tumours suggests that the TAAs exposed by radiotherapy may not be present at tumours in other anatomical locations or even if they are present may only be recognised in subgroups of the tumour and not the entire cellular population thereby making immune clearance at other anatomical locations greatly limited. Furthermore, even for TAAs that are shared sufficiently, the CD8+ T-cells may not be able to access tumours at all sites due to localised immunosuppressive effects. Therefore, Brooks et al.[42] argue that, since each irradiated tumour provides an independent opportunity for disease release of distinct TAAs and the immune activation is also limited by each organ and the surrounding tumour microenvironment, the irradiation of multiple disease sites can potentially improve the promotion of antigen presentation, improve the level of immunological 'visibility' at all tumour sites, increase the likelihood of exposure and priming to desired shared TAAs, reduce the immunosuppressive barrier effects of bulky lesions in all areas of disease and increase the probability of systemic activation of anti-tumour immunity. They further expressed that comprehensive multi-site radiotherapy would enable the elimination of heterogeneous and resistant tumour clones when ablative doses are used, providing a solution to immune-checkpoint inhibition resistance. In this regard, they proposed combined radiotherapy to muli-tumour sites with immune-checkpoint inhibition that will result in a robust localised anti-tumour immune response at each site and the localised activation of the immune system by radiation at each site when combined will potentially lead to an effective systemic effect and the destruction of tumours at the unirradiated sites that share the similar locally primed antigens.

The Effect of the Timing of Immunotherapy on Radiotherapy Induced Abscopal Response

Some studies[24,30,34,44–47] have reported that the timing for the application of the immunotherapy can potentially impact the efficacy of radiation to induce an abscopal response in cancer patients. Buchwald et al.[30] reported that the effect of sequencing of immunotherapy to enhance the abscopal effect is dependent on the mechanism of the immunotherapy drug being used and that recent preclinical tumour data demonstrate that initiating anti-programmed death-ligand 1 (PD-L1) 7 days following radiotherapy was inferior to starting on either the first or the last day. They proposed that anti-PD-1/PD-L1 and radiotherapy should be given concurrently otherwise radiotherapy should precede the administration of checkpoint blockade. They elucidated that radiotherapy delivered to the tumour following anti-PD-1/PD-L1 may obliterate the infiltrated and reinvigorated T-cell response. However, if radiotherapy is delivered before the anti-PD-1/PD-L1, the radiotherapy stimulated naïve T-cell differentiation will synergise with checkpoint blockade and radiotherapy-induced T-cell death of anti-PD-1/PD-L1 reinvigorated T-cells may be avoided.[30] Young et al.,[44] on the other hand, analysed the optimal timing of anti-CTLA-4 blockade and anti-OX40 immunotherapy with radiotherapy for optimal tumour control in CT26 murine colorectal carcinoma mice model. The tumour-bearing mice were treated with radiotherapy to a dose of 20 Gy

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delivered only to the tumour and combined with either the anti-CTLA-4 antibody or anti-OX40 agonist antibody immunotherapy delivered at a single time-point around the radiotherapy delivery. They observed variations in the optimal timing of the therapies and reported that anti-CTLA-4 was very effective when given prior to radiation therapy, administration of anti-OX40 agonist antibody was optimal when delivered 1 day following radiation and a combined treatment of anti-CTLA-4, radiotherapy and anti-OX40 using the ideal timings in a transplanted spontaneous mammary tumour model showed complete cure of the tumours. They concluded that a combination of immunotherapy and radiotherapy results in improved therapeutic efficacy and that the ideal timing of administration with radiotherapy is dependent on the mechanism of action of the immunotherapy employed. Frey et al.[24] used a carcinogen-induced murine colon carcinoma CT26 colon adenocarcinoma cell model to investigate the pathways of immune cell infiltration into colorectal tumours after local hypofractionated radiotherapy to evaluate the optimal timing for the addition of immune modulations and radiotherapy breaks to protect infiltrating immune cells. They reported that hypofractionated radiotherapy potentially activates dendritic cells, produces elevated levels of tumour-infiltrating macrophages and antigen-presenting cells and adaptive immune cells into solid tumours; however, the presence of immune cells in the tumour which are useful for anti-tumour immune responses is time dependant.

Enhancement of Radiotherapy-Induced Abscopal Response with Immunotherapy

Reports on abscopal effects following radiotherapy have been very limited in the past, however, the recent developments in immunotherapy have allowed this effect to become more prevalent and has incited a lot of research interest. The potential expectation is that the combination of radiotherapy and immunotherapy could expand the role of radiotherapy from a purely local tumour control treatment to also play a significant role in advanced and metastatic tumour control. Several studies[28,30,34,36,44,48] have reported that radiotherapy-induced abscopal response rates can be significantly enhanced with the addition of immunotherapy, suggesting that radiotherapy can increase the immunogenicity of a tumour and can, therefore, increase the effectiveness of immunotherapy. According to Morales-Orue et al.,[48] the combination of radiotherapy and immune checkpoint inhibitors can augment the inducement of abscopal response and improve cancer patients' survival rates. They elucidated that the immune checkpoint inhibitor drugs target the CTLA-4 and PD-1/PD-L1 checkpoint pathways and as a result are elevated in anti-tumour immune response due to disruptions in inhibitory signalling. Furthermore, the irradiated tumour will likely signal immunogenic cell death and promotes antigen presentation and diversity, which can enhance the generation of anti-tumoural immunity and the radiotherapy and immune checkpoint inhibitors together can further promote the priming of the anti-tumour immune response.[30,48]

Enhancing abscopal effects with PD-1 inhibitors

Trommer et al.[29] conducted a retrospective single-center study to evaluate the abscopal response in 168 patients with metastatic tumours treated between 2013 and 2017 with radiation therapy and simultaneous PD-1 inhibition with pembrolizumab or nivolumab. They reported that out of 24 patients who were eligible for tumour analysis for an abscopal response, they observed that 29% (7/24) of the patients exhibited the abscopal effects. They concluded that their results represent a further step towards a possible application of radiation therapy together with immune checkpoint inhibition in patients with advanced cancer stages to induce an abscopal effect that enables a more efficient long-term immune response after radiation therapy. Park et al.[49] investigated the influence of PD-1 expression on the abscopal effect anti-tumour response induced by SABR in preclinical melanoma and renal cell carcinoma models. They compared the SABR-induced anti-tumour response in PD-1-expressing wild-type and PD-1-deficient knockout mice. They observed that a combination of SABR with PD-1 blockade therapy elicited a 66% reduction in the size of unirradiated, secondary tumours that were outside the SABR radiation field portal and the observed abscopal effect was tumour-specific and was not dependent on tumour histology or host genetic background. They concluded that SABR induces an abscopal tumour-specific immune response in both the irradiated and unirradiated tumours, which is potentiated by PD-1 blockade and the combination of anti-PD-1 blockade and local radiotherapy could be of significant clinical interest because they can lead to the systemic control of tumours that are refractory to treatment with PD-1 blockade alone. Furthermore, a single SABR and short-term PD-1 blockade may focus the anti-tumour T-cell response in the targeted tissues and be less likely to elicit an autoimmune reaction in other organs.

Enhancing abscopal effects with CTLA-4 inhibitors

Studies[12,28,34,41,50–54] have reported that the immune checkpoint inhibitor, CTLA-4 can potentially enhance the systemic anti-tumour response of radiotherapy and improve the efficacy of abscopal response. Vanpouille-Box et al.[50] investigated the mechanisms by which precision radiotherapy synergises with anti-CTLA-4 antibody to induce anti-tumour T-cells against poorly immunogenic tumours using a mice bearing bilateral TSA mammary carcinoma model. They reported the observation of abscopal responses in mice treated with 8 Gy in three fractions in combination with anti-CTLA-4, and also the anti-CTLA-4 treatment led to a significant improvement in control of the treated tumour. They also reported that radiation-induced activation of type-I interferon pathway correlates with the ability of the radiation to induce abscopal responses in combination with anti-CTLA-4. Golden et al.[52] reported on the abscopal response in a 64-year-old male smoker who presented with stage-IV lung cancer and was treated with radiotherapy and an anti-CTLA-4 monoclonal antibody, ipilimumab. The irradiated target was the most metabolically active liver mass which was treated to a total dose of 30 Gy in five fractions. They reported observing an increase in tumour-infiltrating cytotoxic lymphocytes, regression of the treated target, a significant decrease in the metabolic activity and size of the metastatic unirradiated tumours and no evidence of disease 1 year after the patient's treatment. Formenti et al.[54] investigated the mechanisms underlying an abscopal response to radiation therapy and ipilimumab, by analysing patient's tumour tissue and peripheral blood and observed that radiation therapy in combination with CTLA-4 blockade induces an abscopal response in chemo-refractory metastatic non-small-cell lung cancers. They expressed the potential of using ipilimumab and radiotherapy for the treatment of metastatic non-small-cell lung cancer via the abscopal response.

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Enhancing Abscopal Effects by Targeting APC Activation

According to Suek et al.[15] ionising radiation induces the abscopal effect at the treated tumour site by two parallel changes such as the release of TAAs and the release of DAMP. The DAMP which activates antigen-presenting cells may include High Mobility Group Box Protein 1 (HMGB1), Adenosine triphosphate (ATP) and non-nuclear DNA. Furthermore, they reported that the release of tumour antigens at baseline plays a significant role in mediating the abscopal effect and therapies that target the activation of antigen-presenting cells could potentially enhance the abscopal response. Pitt et al.[55] reported that when ionising radiation induces damages in the DNA of a tumour cell, it can result in immunogenic cell death in which the tumour cell releases antigen and enhances phagocytosis by antigen-presenting cells through calreticulin signalling, dendritic cells and macrophages resulting in the presentation of tumour antigens by antigen-presenting cells. However, antigen presentation by immature dendritic cells can lead to T-cell tolerance as T-cells become anergic, suppressive, or are deleted. Suek et al.[15] reviewed toll-like receptor agonists 9 (TLR9) and the cluster of differentiation 40 (CD40) agonists therapies targeted at antigen-presenting cells activation as promising therapeutic targets to enhance abscopal effects. They expressed that therapies involving cytosine-phosphorothioate-guanine (CpG) oligonucleotides induced highly potent abscopal responses in mouse studies, which usually resulted in complete regression of both the treated tumours and distant non-treated tumours. Furthermore, they reported that TLR9 agonists, as monotherapy have been demonstrated in several phases I and II trials and resulted in both objective and complete response in cutaneous T-cell lymphoma, basal cell carcinoma and melanoma.[15] They also reported that agonist CD40 antibodies have shown to be effective at regressing tumours in preclinical models, have also shown moderate therapeutic activity in the clinic and several are currently in active clinical development. Moreover, CP-870,893 (CD40 agonist) as a single agent has resulted in a 14% objective response rate in a study of advanced solid cancers and in combination with chemotherapy has had a 20% response rate in various advanced solid tumours.[15]

Case Reports on Abscopal Effects Observed in Patients

Azami et al.[16] presented a rare case of a 64-year-old woman diagnosed with breast cancer and multiple bones, lung, and lymph node metastasis, in whom the abscopal effect was observed after radiotherapy had induced an anti-tumour response in all metastatic lesions, without a combination therapy. The patient received localised radiotherapy of 60 Gy to the right breast, 28 Gy to the left femur, and 39 Gy to the lumbar vertebrae and sacrum which were metastatic sites associated with intense pain. They reported that a follow-up after 10 months following radiotherapy showed a dramatic disease remission, determined as a complete response, was observed in all the irradiated sites and in all other sites originally exhibiting abnormal fluorodeoxyglucose uptake but were not irradiated and at 21 months later, bone metastases were stable and there were no metastases in internal organs.[16] Brenneman et al.[17] reported a case study of a 67-year-old female with inoperable rapidly progressive metastatic retroperitoneal sarcomas disease treated with palliative proton radiotherapy to the primary tumour site. They indicated that following the completion of radiotherapy, the patient demonstrated complete regression of all unirradiated metastatic sites consistent with the abscopal response, and the near-complete response of the primary tumour without additional therapy.[17] Britschgi et al.[18] also reported on a 47-year-old male smoker who was diagnosed with lung adenocarcinoma and was treated with combination chemotherapy and cetuximab followed by radiotherapy with cetuximab and surgical resection. A pathological complete response was achieved, but retroperitoneal lymph node relapse occurred 8 weeks post-operative and the patient was then enrolled in an expanded access program of an anti-PD-1 monoclonal antibody, nivolumab, which resulted in regression of the initial sites but three new abdominal lymph node metastases appeared. The patient was then treated for the oligo-progression using Stereotactic Body Radiation Therapy (SBRT) with two out of the three metastatic lymph nodes treated to 6 Gy in three fractions at 80% isodose line and with nivolumab treatment. A PET/CT scan 10 weeks after SBRT showed a complete radiological and metabolic response consistent with an abscopal response provoked by PD-1 targeting in combination with SBRT.[18]

Garelli et al.[19] reported on the observation of abscopal response in case studies of three patients with metastatic lung cancer were treated with immunotherapy and fractionated radiotherapy. The first case was a 54-year-old male presented with pulmonary large cell neuroendocrine carcinoma of the right upper lobe with bilateral adrenal metastases who received the first-line treatment of four cycles of pemetrexed, cisplatin and bevacizumab chemotherapy, but the tumour progressed in the right upper lobe and both adrenal glands. However, post-operative radiotherapy delivered at 3 Gy in ten fractions to the second and third thoracic vertebrae combined with nivolumab showed partial regression of the lung tumour and the out of field adrenal metastases.[19] The second case was a 64-year-old male diagnosed with central adenocarcinoma of the left upper lobe with a brain and ocular metastasis who was treated with four cycles of nab-paclitaxel/carboplatin with atezolizumab followed by four cycles of atezolizumab alone and showed a good response of the ocular metastasis but the brain metastasis progressed. However, whole-brain radiotherapy delivered at 3 Gy in ten fractions combined with atezolizumab monotherapy exhibited a partial response in the brain tumour and complete remission of the out of field lung and mediastinal tumour masses. The third case was a 70-year-old male with central adenocarcinoma of the middle lobe with positive mediastinal lymph nodes and malignant ipsilateral pleural effusion who received first-line therapy with pembrolizumab and resulted in a partial response, but the pulmonary and pleural disease progressed and symptomatic brain metastasis associated with perimetastatic cerebral oedema developed after a year of treatment. However, whole-brain radiotherapy delivered at 3 Gy in ten fractions combined with pembrolizumab resulted in partial regression of the out of field lung tumours and pleural effusion. Nam et al.[20] reported on a 65-year-old patient with hepatocellular carcinoma and metastasis of the frontal bone mass that regressed after radiotherapy for frontal bone mass without any other treatment. The patient received radiation therapy to the frontal skull to a total dose of 30 Gy and 10 months follow-up showed a marked reduction in the size of the hepatic mass and a reduction in a number of nodules. A further 3 months follow-up showed additional degradation in the size and number of nodules of the tumour and complete disappearance of the skull mass. Lakshmanagowda et al.[10] also reported on an abscopal response in a 65-year-old female patient with chronic lymphocytic leukemia following radiotherapy. The patient presented with a massive right axillary lymphadenopathy, with multiple lymph nodes and multiple bilateral cervical lymph nodes and was treated with local radiotherapy to the axilla to a dose of 24 Gy in 12 fractions. After 1 week, the unirradiated lymph nodes in the

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neck and away from the treatment field regressed and by the end of the treatment, the lymph nodes completely regressed consistently with the abscopal response.[10]

Conclusions

Radiotherapy-induced abscopal effects have been observed in patients but are still relatively rare, have been described in preclinical settings and have recently gained extensive interest in both preclinical and clinical studies. The effect has become very relevant and clinically meaningful in cancers due to recent development and use of immunotherapy strategies incorporating combinations of targeted immunomodulators and immune checkpoint blockade with radiotherapy. The enhancement of cancer immunotherapy, especially immune checkpoint inhibitors, could potentially enable the translation of the abscopal effect into the clinics as a new strategy to induce therapeutically effective anti-tumour immune responses in cancer patients. The combination of radiotherapy and immunotherapy has the potential to expand the role of radiotherapy from a purely local tumour control treatment to play a significant role in advanced and metastatic tumour control and this could likely lead to a paradigm shift in the treatment of patients with metastatic cancer.

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Conflict of Interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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