

Research Progress and Existing Problems for Abscopal Effect

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Abstract: Radiation therapy plays a vital role in the treatment of tumours. In particular, the occurrence of the “abscopal effect” brings about a favourable turn for the treatment of patients with advanced metastatic malignant tumours. Because of the abscopal effect, non-irradiated areas are also treated. However, the abscopal effect occurs by chance, not through seeking. Although the abscopal effect has been studied enthusiastically, the desired result does not appear to be achieved. Moreover, its combination with immunotherapy appears to be overwhelming. There is an opinion that abscopal effect is difficult to achieve by irradiation of a single tumour, and irradiation of multiple or total lesions is advocated to increase the possibility of obtaining clinically meaningful outcomes. Obviously, there are still questions about the mechanism, condition and possibility underlying the occurrence of the abscopal effect. Can the abscopal effect truly change the future treatment strategy as the researchers expect? What are the current problems? This article reviewed the research in recent years to explore the progress and controversy surrounding the abscopal effect of radiation therapy.

Keywords: radiation therapy, abscopal effect, immunotherapy, immunomodulation, tumour microenvironment

Following palliative pain relief or systemic treatment, patients with advanced malignant tumours often receive radiation therapy for the purpose of local control of lesions in a single organ or site. However, radiation therapy is often powerless to treat lesions outside the irradiation field. The existence of the “abscopal effect” brings a glimmer of hope. The concept of the abscopal effect originated in 1953. Mole et al found that the irradiation of local tissues induced biological responses in the same or different types of tissues far away from the radiation site and therefore proposed this concept. However, the abscopal effect still “comes by chance, not through seeking”. A melanoma case report by the Memorial Sloan Kettering Cancer Centre in 2012 implied the possibility of immune checkpoint inhibitors to induce the abscopal effect.¹ The patient underwent palliative radiation therapy for metastatic thoracic lesions after treatment with immune checkpoint inhibitors. Interestingly, other metastatic lesions also shrank. Doctors examined the changes of immune biomarkers in the peripheral blood to verify the relationship between the abscopal effect and immunity. Similar to throwing a stone into water, this case aroused great enthusiasm for the subsequent study of such phenomena. However, subsequent studies found that the abscopal effect failed to achieve the desired results. Questions remain about the mechanism, condition, and possibility underlying the occurrence of the abscopal effect. This article intends to provide an overview of these questions.

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The Potential Mechanisms Underlying the Occurrence of the Abscopal Effect

Radiation-Induced Immune Phenomenon

As early as 2004, a study pointed out that the abscopal effect might be mediated by immunity.² Moreover, cellular immunity might play a more important role than humoral immunity.³ After many animal experiments, some researchers hypothesized that radiation therapy introduces ionizing radiation, resulting in the production of inflammatory signals. Cellular stress or damage causes the dying tumour cells to release adenosine triphosphate (ATP), tumour antigens, and danger signals such as high mobility group box 1 (HMGB1) and calreticulin. Radiation also increases the secretion of transforming growth factor beta (TGF- β) and the inhibition of CD4⁺ regulatory T cells (Tregs).⁴ In the context of radiation, the number and diversity of these tumour-associated antigens are significantly increased. The antigens are recognized by Toll-like receptors (TLRs), which activate all components of the immune system⁵ and stimulate the antigen-presenting cells (APCs) to produce tumour-associated antigens.^{6,7} Activated APCs enter the tumour-draining lymph nodes, where they activate naive CD8⁺ T lymphocytes to antagonize the tumour cells presenting these specific antigens.^{8,9} These newly activated lymphocytes are distributed to the entire body via the circulatory system. They can also extravasate at the unirradiated tumour site, resulting in tumour shrinkage in non-irradiated regions. This phenomenon is known as the abscopal effect.

Cytokine Interactions in the Tumour Microenvironment

The changes in the tumour microenvironment are also the key to the occurrence of the abscopal effect after radiation therapy.^{10,11} After radiation therapy, the levels of interferon-gamma (IFN- γ), C-X-C motif chemokine ligand 9 (CXCL9), C-X-C motif chemokine ligand 10 (CXCL10), and C-X-C motif chemokine ligand 16 (CXCL16) are increased.¹² These radiation-induced key chemokines increase T cell motility and vascular permeability, thereby attracting effector T cells to the tumours.^{13,14} The factors produced by radiation therapy are very important for tumour treatment. For example, an exogenous increase of type I IFN is sufficient to mimic the tumour-regression effect of radiation therapy.¹⁵ Interferon-beta (IFN- β) also plays an important role in the

activation of T cells.¹⁶ Radiation therapy-induced IFN- β was also related to the development of the abscopal effect in patients with non-small cell lung cancer (NSCLC).¹⁷ Shortly after the completion of radiation therapy (day 22), serum IFN- β levels in 7 respondents significantly increase from baseline. IFN- β production is closely related to cytosolic DNA. In regard to cytosolic DNA, the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway needs to be mentioned. The cGAS-STING pathway is a component of the innate immune system. Once activated, this pathway promotes the production of cytosolic DNA. Therefore, it is deduced that the interferon-induced cGAS/STING pathway promotes the emergence of anti-tumour T cells.¹⁸ Other previous clinical trials have verified the relationship between the abscopal effect and p53.^{19,20} The downstream pathway of p53 is important for triggering the abscopal effect, which, however, was not further elaborated (Figure 1).

The Factors Promoting the Occurrence of the Abscopal Effect Combination with Immune Factors Increases the Occurrence Probability of the Abscopal Effect

The appearance of “abscopal effect” (Figure 2) indicates that patients can reduce the area of radiotherapy to reduce the side effects of radiotherapy. For this reason, researchers have carried out numerous clinical trials and preclinical studies to explore how to promote the occurrence of the abscopal effect, especially in metastatic tumours. Pfannenstiel et al established two mouse models of metastatic melanoma, representing BRAF mutant and non-mutant tumours.²¹ The combination of radiation therapy and immunotherapy produced a stronger systemic anti-tumour immune response than did immunotherapy alone, which led to a reduction in tumour growth and an increase in the number of activated CD8⁺ cytotoxic T cells. In addition, the abscopal effect was observed in unirradiated tumours and was independent of BRAF status. In another melanoma-related study using the combination of radiation therapy and immunotherapy, administration of the inhibitors of the cytotoxic T lymphocyte-associated antigen (CTLA4) and programmed cell death-ligand 1 (PD-L1) increased the incidence of the abscopal effect.²² Golden et al reported the first case of the abscopal effect in a patient with refractory lung cancer who was treated with radiation therapy and ipilimumab. The patient showed no sign of disease progression even at one year after the concurrent radiation therapy and

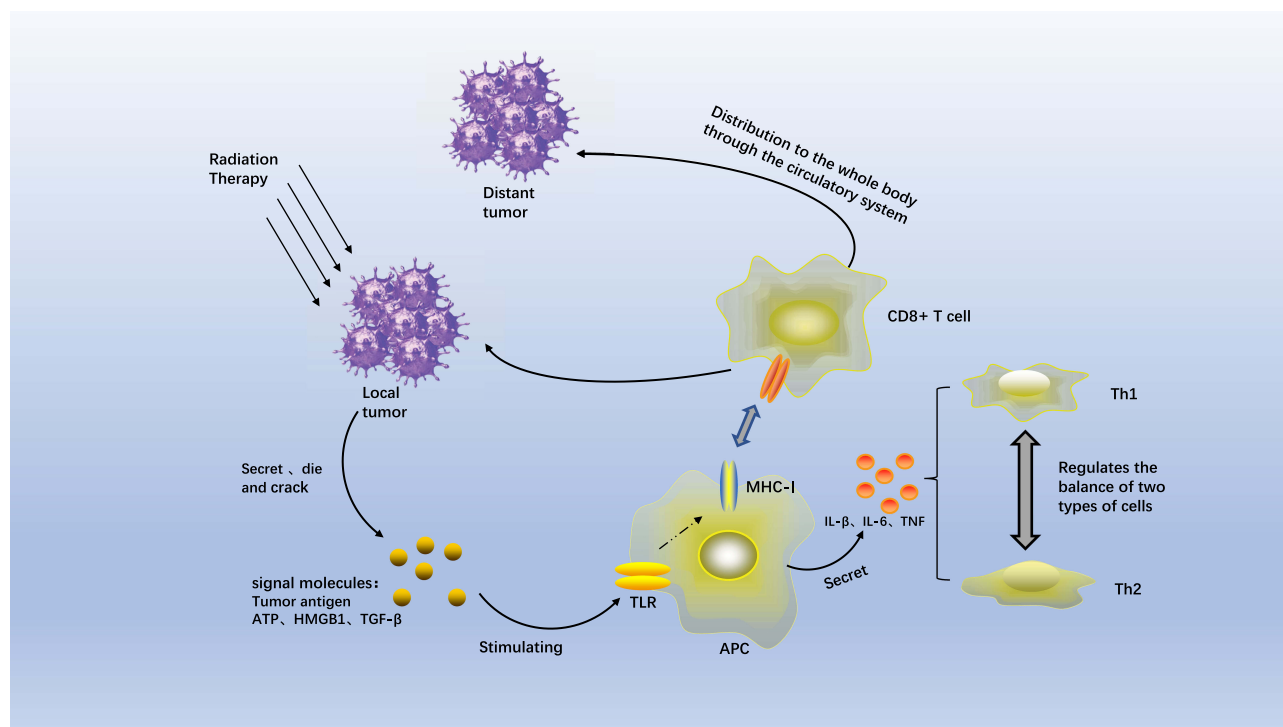


Figure 1 The potential mechanisms underlying the occurrence of the abscopal effect.

ipilimumab treatment.²³ Many clinical and preclinical trials have confirmed that anti-CTLA4 or anti-programmed death-1 (PD1) antibody can be used as immune checkpoint inhibitor to increase T cell activity against tumour cells.^{24–28} The above data demonstrate that the combination of radiation therapy and immune checkpoint inhibitors induces anti-tumour responses to control local and distant diseases.

In addition to combining with immune checkpoint inhibition, the possibility of abscopal effect occurrence can be enhanced through using immunoadjuvants. For example, FMS-like tyrosine kinase 3 ligand (FLT3L) can be used to recruit and stimulate APCs.³ Anti-cluster of differentiation 40 (anti-CD40) antibody can be used to enhance the activation of APCs.²⁹ In a mouse model of pancreatic cancer, anti-CD40 treatment resulted in not only the regression of the untreated contralateral tumours but also the development of long-term immunological memory.³⁰ Administration of the immunocytokine L19-IL2 in combination with radiation therapy (a single dose of 15 Gy) induced the abscopal effect in 20% of the immunocompetent mice with colon tumours.³¹ Administration of the granulocyte-macrophage colony-stimulating factor also promoted the occurrence of the abscopal effect in patients with metastatic cancer.³² The toll-like receptor 7 (TLR7) agonist imiquimod promoted the radiation therapy-elicited in situ vaccination, thereby enhancing the

incidence of the abscopal effect.³³ ECI301 enhanced the anti-tumour effect of radiation and induced the occurrence of the abscopal effect in mice.³⁴ New technologies developed in recent years, including the multifunctional smart radiation therapy biomaterials (SRB) loaded with CD40mAb, also enhance the abscopal effect.³⁵ Antigen-capturing nanoparticles (AC-NPs) delivered tumour-specific proteins to APCs and significantly enhanced the efficacy of anti-PD-1 treatment, thereby inducing the abscopal effect.³⁶ In lymphoma,³⁷ renal cell carcinoma,³⁸ breast cancer,³⁹ hepatocellular carcinoma,⁴⁰ prostate cancer,⁴¹ pancreatic cancer,⁴² and other metastatic solid tumours,³² the abscopal effect also occurred after the combined application of immunotherapy and radiation therapy. In addition to the differences in the immune drugs or adjuvants utilized, another noteworthy point is the mode of administration. Local delivery of immunotherapeutic drugs into the tumours leads to increased local drug concentration, and the odds of abscopal effect occurrence are also increased.⁴³

Appropriate Radiation Therapy Mode Increases the Occurrence Probability of the Abscopal Effect

The immune response to radiation therapy is inextricably linked to tumour types, immunomodulation, and dose and mode of radiation therapy. Ionizing radiation delivered by

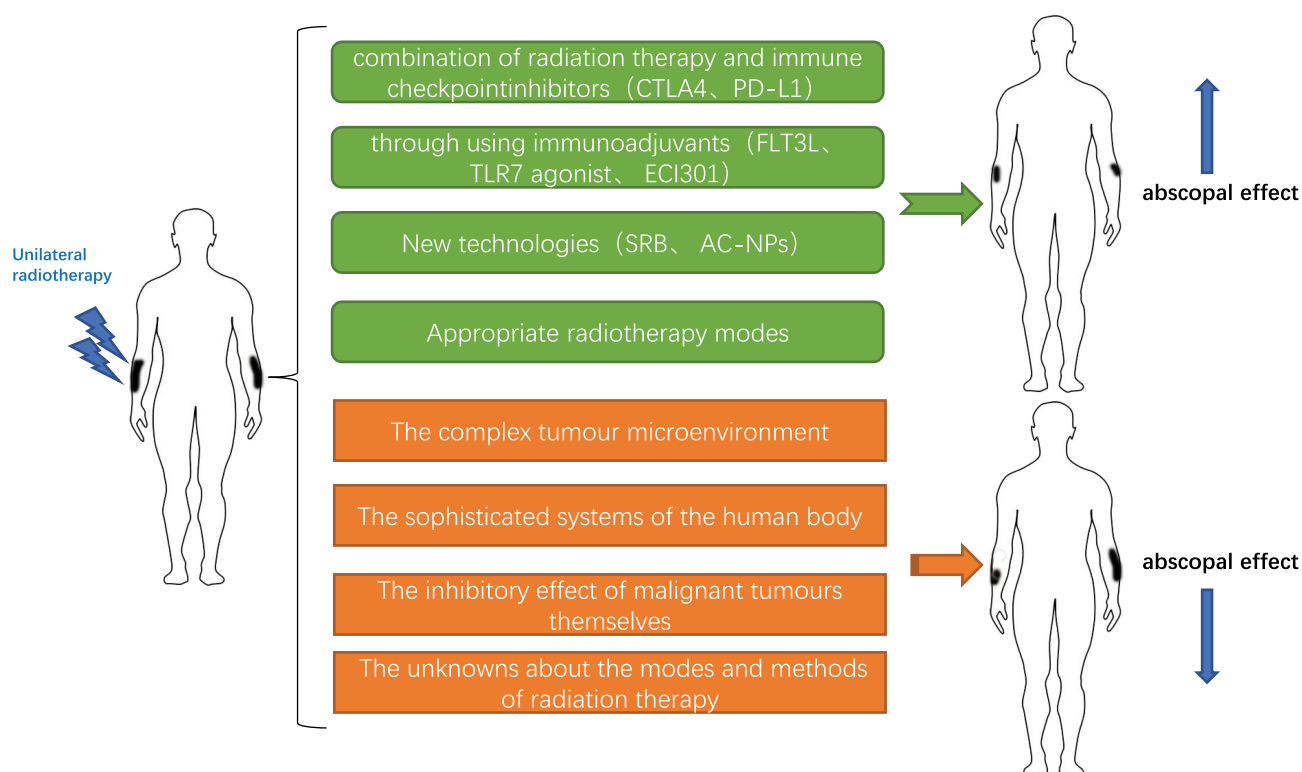


Figure 2 Conditions that induce or limit the occurrence of the abscopal effect.

radiation therapy induces DNA damage, leading to the apoptosis, senescence, and autophagy of tumour cells.⁴⁴ Lymphocyte levels are reduced after radiation therapy.^{45,46} However, low doses of radiation appear to activate macrophage but do not induce cell death, while high doses of radiation appear to induce immunogenic effects.⁴⁷ In a preclinical trial, low-dose radiation increased the infiltration of T cells into the irradiated area.⁴⁸ Radiation therapies using higher doses are more likely to cause increased DNA damage and expose more antigens, thereby enhancing the immune response. However, excessive radiation doses are more harmful than beneficial to the patients. Is there a suitable optimal radiation dose that maximally activates the immune response in patients while promoting the occurrence of the abscopal effect? To explore this dose, Professor Poleszczuk established a mathematical model. The model suggested that the optimal radiation doses per fraction were between 10 and 13 Gy, at least under the experimental setting used for model calibration.⁴⁹ However, in reality, researchers believe that radiation therapy doses ranging from 2 to 20 Gy may trigger immunogenic cell death.⁵⁰ A pre-clinical trial showed that a combination of low-dose-fractionated radiation therapy and immunotherapy was

more likely to trigger the abscopal effect.²⁵ In contrast, high-dose-hypofractionated radiation therapy was more conducive to survival in a tumour mouse model.⁵¹ In clinical cases of the abscopal effect, a hypofractionated dose of 30 Gy was delivered in 5 fractions or a total dose of 28.5 Gy was delivered over 3 fractions.^{1,23} Another study showed that radiation-induced changes in the content of the DNA exonuclease Trex1 (three prime repair exonuclease 1) in various cancer cells.⁵² Trex1 degrades the DNAs in the cytosol to attenuate their immunogenicity, thereby reducing the immune response.⁵³ Therefore, it is necessary to identify proper radiation doses that will not induce Trex1. Repeated irradiation with these doses will increase the content of cytosolic DNA. Further amplification of interferon- β will lead to the recruitment and activation of Batf3-dependent dendritic cells (DCs), which is also very important for the occurrence of the abscopal effect.

In addition, radiation therapy induces anti-tumour immune response, which usually depends on the immunogenicity of the tumours. Tumour immunogenicity varies greatly among different individuals, different types of cancers, and even the same type of cancers.^{1,54} High immunogenicity is more potent in stimulating immunity. Moreover,

Table I Clinical trials or cases with abscopal effect

Years	Tumors	Radiation therapy	Immunotherapy	Sequence of RT and immunotherapy	Reference
2014	Melanoma	RT of brain metastasis or extracranial sites	Anti-CTLA-4 (ipilimumab, 3 mg/kg/3 weeks)	RT after ipilimumab	[¹⁰⁵]
2015	Metastatic solid tumors	35 Gy/10 fractions	GM-CSF (125 µg/m ² /2 weeks)	Concurrent	[³²]
2015	Melanoma	Lung/bone 8 Gy × 2 or 8 Gy × 3 Liver/subcutaneous 6 Gy × 2 or 6 Gy × 3	Anti-CTLA-4 (ipilimumab)	RT before ipilimumab	[²²]
2016	Melanoma	SBRT	Anti-CTLA-4 (ipilimumab, 3 mg/kg/3 weeks)	Concurrent and post-radiation	[¹⁰⁶]
2017	Melanoma	30 Gy/10 fractions	Anti-PD-I (pembrolizumab, 2 mg/kg/3 weeks or nivolumab, 3 mg/kg/3 weeks)	Concurrent	[¹⁰⁷]
2017	Melanoma	Conventional external beam radiation and stereotactic radiosurgery	Anti-CTLA-4 (ipilimumab, 3 mg/kg/3 weeks)	Concurrent	[¹⁰⁸]
2018	Advanced cancer	Stereotactic ablative RT	DC vaccination and TLR-3 agonist	Concurrent	[¹⁰⁹]
2018	Metastatic breast cancer	22.5 Gy/3 fractions	Anti-TGFβ (fresolimumab, 1 mg/kg/3 weeks or 10 mg/kg/3 weeks)	Concurrent	[¹¹⁰]
2018	Melanoma	26 Gy/3–5 fractions	Anti-PD-I (pembrolizumab, 2 mg/kg/3 weeks or nivolumab, 3 mg/kg/2 weeks)	Concurrent and post-radiation	[¹¹¹]
2018	Metastatic NSCLC	Phase I: 6 Gy × 5/fractions Phase II : 9.5 Gy × 3/fractions	Anti-CTLA-4 (ipilimumab, 3 mg/kg/3 weeks)	Concurrent	[¹⁷]
2018	Refractory Hodgkin's Lymphoma	total 40 Gy in 20 fractions, mediastinal nodes	Anti-PD-I (Nivolumab, 2 doses)	Concurrent and post-radiation	[¹¹²]
2018	Prostate cancer	SABR	Hiltonol intratumoral injections (DC Local ReactionGI)	Concurrent	[¹⁰⁹]
2019	Unresectable stage IIIB/IV bulky NSCLC	SBRT-PATHY	None	None	[¹¹³]
2019	Renal cell carcinoma	high-dose-rate interstitial brachytherapy (HDR-ISBT)	Anti-PD-I (Nivolumab infusions of 240 mg /alternate week)	Nivolumab was restarted nine days after HDR-ISBT.	[¹¹⁴]

immunogenicity level is related to prognosis. The immunogenicity of tumours induced by different modes of radiation therapy varies considerably. Current combination therapies

aim to stimulate and enhance immunogenicity to the greatest extent.^{55,56} The nature of the radiation ray cannot be ignored. High linear energy transfer (LET) radiation mainly

acts directly on the biological macromolecules in the tissues and cells, causing damage. The physical characteristic of high-LET radiation is the presence of Bragg peaks, while the biological characteristics of high-LET radiation include high relative biological effect and low oxygen enhancement ratio. Low-LET radiation mainly acts indirectly. Because organisms are in a high-water environment, low-LET radiation interacts with the water molecules in the biological tissues, generating free radicals. These free radicals then interact with biological macromolecules and damage them. Low-LET radiation can be used to achieve non-discriminatory killing of tumour cells that display heterogeneous radiosensitivity due to the different oxygen content in tumours.⁵⁷ In a review, Professor Pouget proposed the idea of complex DNA damage leading to immune signal transduction: clustered DNA damage will eventually cause persistent DNA damage, leading to cell aging or cell death (ie, apoptosis), triggering different “dangerous” signals or damage-associated molecular patterns (damps: ATP, short DNAs/RNAs, ROS and others). In terms of targeted radionuclide therapy, Proton/carbon ion radiation therapy and alpha-particles deliver high-LET radiation.⁵⁸ Low energy γ ray or carbon ion and coradiation elicit the abscopal effect, which is closely related to macrophages.⁵⁹

Exploration of the Cause That Prevents the Occurrence of the Abscopal Effect

Numerous clinical trials and basic research aim to promote the occurrence of the abscopal effect (Figure 2). In reality, however, the odds of abscopal effect occurrence have not reached expectations.⁶⁰ Combined administration of radiation therapy and immunotherapy improves the occurrence rate of the abscopal response compared to radiation therapy or immunotherapy alone. However, the overall occurrence rate of the abscopal effect remains unsatisfactory, which indicates its limitations. A systematic review found that there were only 46 documented cases of abscopal effect of radiation therapy between 1969 and 2014.⁶¹ A study conducted in Brazil explored the probability of abscopal effect occurring after anti-PD1 therapy and associated radiation therapy. The study examined 16 patients, including 12 patients with metastatic melanoma, 2 patients with metastatic NSCLC, and 2 patients with metastatic renal cell carcinoma. Three patients with melanoma developed the abscopal effect, a rate of 18.7%. In contrast, no patients with NSCLC or renal cancer exhibited the abscopal effect.⁶²

We summarized the reasons behind the unsatisfactory rate of abscopal effect occurrence into the following aspects:

The Complex Tumour Microenvironment

The post-radiotherapeutic changes in the tumour microenvironment are not all beneficial. In fact, it is difficult to overcome the inhibitory effect of the tumour microenvironment even if radiation therapy activates the anti-tumour CD8 + T cells,⁶³ and the infiltration of the anti-tumour effectors to tumour tissues remains weak.⁶⁴ The tumour microenvironment is not singular and orderly. Radiation therapy leads to the release of a variety of inhibitory factors, including TGF- β . TGF- β is an immunosuppressive factor. It not only inhibits the immune response by reducing the antigen-presenting capacity of DCs and the activation of effector T cells^{65,66} but also induces radioresistance in tumour cells and decreases their radiosensitivity.⁶⁷ In addition, the appearance of interleukin 6 (IL-6), interleukin 10 (IL-10) and colony-stimulating factor 1 (CSF-1) also promotes tumour cell proliferation and invasion.^{68–70} Their appearance not only reduces the occurrence of abscopal effect but also reduces the efficacy of radiation therapy.⁷¹ However, radiation therapy induces the release of a variety of cytokines such as interleukin 1 beta (IL-1 β), which promote anti-tumour effects.^{72,73} Radiation therapies using different doses and modes will inevitably yield inconsistent outcomes. These facts strongly confirm the complexity and contradictions of various factors in the tumour microenvironment.

In addition, the tumour microenvironment is equally complex at the cellular level. After irradiation, tumours develop a variety of resistance mechanisms that promote tumour recurrence, including the production of suppressive immune cells capable of inhibiting T cell activation. These suppressive immune cells, including Tregs, bone marrow myeloid-derived suppressor cells (MDSCs), and tumour-associated macrophages (TAMs),^{74–76} infiltrate more into tumour tissues after radiation therapy.^{74,77} Tregs are key cells in the maintenance of tumour immune tolerance, and they downregulate immunity and even promote tumour angiogenesis.⁷⁸ In addition, Tregs not only produce a variety of inhibitory cytokines (including tumour necrosis factor β (TNF- β),⁷⁹ interleukin 35 (IL-35),⁸⁰ and IL-10⁸¹) but also preempt IL-2 and reduce the activation of cytotoxic T cells.⁸² MDSCs not only reduce immune activity at the immune level but also promote tumour infiltration and migration.⁸³ TAMs are the main white blood cells that infiltrate solid tumours, comprising up to 50% of the tumour mass. TAMs promote cancer cell proliferation, invasion,

metastasis, and angiogenesis through releasing cytokines, growth factors, extracellular matrix-degrading enzymes, the angiogenic factor prokineticin (Bv8), and matrix metalloproteinase 9 (MMP9).⁷⁶ On the other hand, radiation therapy renders tumour cells more susceptible to immunity. Reits et al found that under high doses of radiation (10–26 Gy), the expression of the major histocompatibility complex I (MHC-I) increased in a dose-dependent manner. Increased MHC-I expression promoted the production of APCs and activated the effector T cells.⁷ It is evident that both the suppressive and the promotive immune cells change after radiation therapy. At present, there is no definite conclusion about which is the dominant type of immune cell. However, the dual nature of the microenvironment and the difficulty of inducing the abscopal effect are implied. In addition to immune cells, tumor stromal cells not only provide physical support for tumor cells but also drive tumorigenicity. Cancer-associated fibroblasts (CAFs) are one of the most important types.⁸⁴ The soluble factors secreted by CAFs induce various phenotypes of adjacent tumor epithelial cells and other stromal cells, and then promote the development of tumor.⁸⁵ Although there is no study on the relationship between CAFs and distant effect, radiation enhances the migration and invasion promoting ability of CAF in vitro and in vivo.⁸⁶

The Sophisticated Systems of the Human Body

As mentioned in the theory of the mechanism of the abscopal effect, radiation therapy leads to the exposure of tumour antigens and the appearance of a “tumour vaccine”, thereby promoting immune activity. However, in reality, the abscopal effect mechanism is far from simple. The human immune system is a sophisticated and complex system. It is difficult to improve the overall effect through one single point or pathway. Moreover, differences exist among individuals, which undoubtedly render it more difficult to induce the abscopal effect. First, the activation of cytotoxic T cells, the cells that actually function in immunity, requires more than the stimulation imposed by the antigen-MHC complex. Other costimulatory signals such as cluster of differentiation 80 (CD80), CD40 ligand (CD40 L), and cluster of differentiation 28 (CD28) are also essential for the activation of CD8⁺ T cells. Such facts indicate that radiation-induced DNA damage and exposure of “tumour vaccine” are not sufficient for stimulation of immunity. A preclinical trial of colon cancer found that systemic

immune enhancement occurred several weeks (rather than immediately) after radiation therapy and was not long-lasting.⁵¹ Poleszczuk et al established a mathematical model.⁸⁷ Examination of virtual cases using this model revealed that the dissemination of activated T cells among multiple metastatic sites was complex, and not all metastatic sites participated equally in systemic immune surveillance. The above findings demonstrate that the likelihood of promoting systemic immunity is rather low. Moreover, the systemic anti-tumour immunity cannot be maintained in the long term even if the abscopal effect has occurred, which is one reason why new radioimmunotherapy strategies are currently being explored.⁸⁸ Finally, application of combination therapy to promote abscopal effect has become a new research hotspot since the discovery of immune checkpoints. However, similar to radiation therapy, immune checkpoint inhibitors and immunological adjuvants may cause a variety of side effects, even highly toxic side effects.^{4,89,90} The combined application of the two will inevitably increase the likelihood of these adverse events.⁹¹ However, PACIFIC and LUN14-179 experiments also confirmed that the incidence of side effects, such as pneumonia, in the study group receiving PD-L1 mAb after concurrent radiotherapy and chemotherapy did not increase significantly compared with the control group. More clinical trials need to be conducted to determine how to minimize the additive toxic effect of radiation and immunotherapy^{4,92} and optimize the order of these two types of treatments. Proper selection of immune checkpoint inhibitors/immunological adjuvants, timing of administration, mode of administration, dosage, and mode of combination are critical to the success of radiation therapy and immunotherapy. However, there is still a lack of definite answers to these questions. These questions further indicate the difficulty of inducing abscopal effect.

The Inhibitory Effect of Malignant Tumours Themselves

Malignant tumour cells exhibit extremely strong mutability, heterogeneity, and atypia, which also increase the difficulty of eliciting the abscopal effect. Studies have shown that the genetic mutations in the primary lesion are not completely consistent with the genetic mutations in the metastatic lesions. Because the local antigen is not necessarily identical to the distant antigen, the immune responses induced by simply targeting local antigens are likely to be ineffective. With the enrichment of the

therapeutic approaches aiming to boost immunity, cancer cells have evolved a series of immune-resistance mechanisms that facilitate their evasion of anti-tumour immune responses. This process is known as immunoediting.^{93,94} Immunoediting downregulates vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1), resulting in the enhancement of the tumour vasculature capable of inhibiting T cell colonization and migration. Immunoediting also leads to the downregulation of the major histocompatibility complex (MHC) and the promotion of suppressive immune cell infiltration. In addition, hypoxic regions are present in some tumours, which may induce immunosuppression through causing immune cell failure.⁹⁵ For example, hypoxia alters the antigen-presenting ability of APCs.⁹⁶ Even if the immune cells that are capable of targeting distant metastases are produced, it is unclear whether these immune cells can smoothly pass through various barriers and successfully reach the targeted area. As demonstrated by studies, the ability of immune cells to accurately reach non-irradiated areas may be one of the rate-limiting steps that trigger the radiation-induced abscopal effect.⁸⁷ These complex interactions contribute to the development of cancer cells and further limit the effect of immunotherapy.^{97,98} Even so, the immune system can still recognize and eliminate cancer cells. However, in the cases in which the metastases contain a large number of tumour cells, the limited number of immune cells is a drop in the bucket. Moreover, patients with advanced cancer have more or less impaired immune functions and compensatory ability. The patients often receive concurrent chemotherapy,⁹⁹ while one of the side effects of chemotherapy is immunosuppression. The integrity of the host immune system determines the sensitivity of the tumours to radiation therapy.¹⁰⁰ Therefore, the above factors also limit the occurrence of the abscopal effect.

The Unknowns About the Modes and Methods of Radiation Therapy

Many studies are striving to identify the optimal radiation therapy dose for induction of the abscopal effect. However, fractionated radiation therapy fails to diversify the T cell receptor repertoire in the distal non-irradiated areas.^{22,101} The above information suggests that the differences in radiation therapy dose, the employed fractionation schemes, and the size and location of the irradiated lesions are also factors influencing the occurrence of the abscopal

effect.^{87,102} To explore the optimal conditions for the induction of the abscopal effect, radiation therapy needs to be standardized.¹⁰³

A Correct View of the Abscopal Effect

Radiation therapy and immunotherapy both occupy pivotal positions in cancer treatment. Currently, numerous clinical studies have explored the combinations of radiation therapy and immunotherapy. A large number of clinical trials and data show that the combination of the two types of treatments not only alleviates the related symptoms of tumour patients and effectively prolongs survival time but also enhances the possibility of abscopal effect occurrence. Will immunotherapy be overly used? Whether the evaluation of curative effect of the combination of two treatment strategies based on the standard RECIST standard is a little single? More than 90% of these clinical studies attempted to induce clinically significant abscopal effects by irradiating individual tumours for the purpose of controlling all tumours. However, Brooks and Chang proposed that the abscopal effect was difficult to achieve by irradiating single tumours. They advocated irradiating multiple or all lesions to increase the likelihood of obtaining clinically meaningful outcomes.¹⁰⁴ There are still questions and controversies surrounding the mechanisms and existence of the abscopal effect. However, the combination of the treatment methods is undoubtedly beneficial to patients. Perhaps there should be more preclinical studies to determine how to better combine radiation therapy and immunity, such as T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and indoleamine 2,3-dioxygenase (IDO), which suppress immune signals, as well as OX40 and 4-1BB, which activate immune signals. Questions still need to be addressed, such as whether it is possible to combine these signalling pathways with different radiotherapy modes to improve the patients' survival and quality of life, and how to weigh the benefits and harms elicited by single-site radiotherapy and multi-site /whole body radiotherapy. Because of the unaddressed questions, the occurrence of the abscopal effect is still unclear. We look forward to subsequent studies and better methods to bring about improved and more beneficial treatments.

Disclosure

The authors declare no potential conflicts of interest.

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