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Systemic Effects of Radiation Therapy-Induced Abscopal Responses in Patients with Advanced Lung Cancer

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Abstract
Background: Out-of-field tumor regression effects of radiation therapy (abscopal response) have been sporadically observed in the past, but they have only recently gained significant importance due to the use of innovative high-precision radiation delivery devices for the treatment of various cancers including non-small cell lung cancer (NSCLC). In this study, we provide a detailed overview of the current state of knowledge and clinical experience of radiation therapy-induced abscopal effects in patients with advanced NSCLC. ***Summary:*** 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 clinical data on the abscopal effect of radiation therapy were reviewed and the outcomes have been summarized. Most studies describing the abscopal effects of radiation therapy in patients with advanced NSCLC have been in the form of either case reports or small cohort studies. Although the exact molecular mechanisms for the abscopal effect are yet to be established, current evidence indicates that tumor cell destruction induced by local radiation therapy releases tumor antigens, which stimulate the immune system of the host to activate the body's immune effector cells systemically and trigger the regression of distant nonirradiated cancer cells. These off-target antitumor effects of radiation therapy provide an opportunity to explore the use of the radiation therapy in combination with novel immunotherapy agents to maximize treatment outcomes in patients with advanced NSCLC and other cancers. ***Key Message:*** The findings suggest that radiation therapy has the ability to induce abscopal effects with an increased potential to boost these effects when it is used in combination with immunotherapy for the treatment of patients with advanced NSCLC and other cancers. Clinical trials investigating radiation therapy-induced abscopal effects may lead to a dramatic change in its use especially when it is combined with immunotherapy for the treatment of patients with advanced NSCLC.

Introduction

Lung cancer continues to be the leading cause of cancer mortality worldwide, accounting for over 1.6 million deaths each year [1–3]. In the USA, lung cancer is the second most common cancer with an estimated 228,000 new

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cases and 143,000 deaths in 2018 [4]. Non-small cell lung cancer (NSCLC) accounts for 85% of the newly diagnosed cases of the lung cancer [5, 6]. Over 70% of the NSCLC patients present with locally advanced or disseminated disease at the time of their diagnosis and are not appropriate candidates for surgery [7]. The majority of NSCLC patients present with locally advanced inoperable or metastatic disease, which in the past made their cancer incurable, and almost all of these patients died from their disease. Patients with NSCLC have a predilection for distant metastasis, and this is associated with a poor prognosis [4]. Until relatively recently, over half of the patients diagnosed with lung cancer died within 1 year of their diagnosis [8]. In general, the prognosis of patients with advanced NSCLC is generally considered poor. Thus, the management of patients with locally advanced or metastatic NSCLC remains challenging.

Despite innovative treatment advances, no significant changes in the survival rates of advanced lung cancer patients have been seen during the last three decades. Brain metastasis is a common problem in patients with metastatic NSCLC, and the long-term clinical outcomes of these patients are generally poor. Between 2007 and 2013, the 5-year overall survival rate for patients with metastatic NSCLC was just only 5.2% [9]. However, the success of new immunotherapeutic agents such as ipilimumab, nivolumab, pembrolizumab, and other immunotherapies has heralded a new era in the effective treatment of metastatic NSCLC. Although immunotherapeutic advances have improved the overall survival rates, there is still a tremendous need for additional strategies to optimize the systemic treatment responses and benefits in patients with metastatic NSCLC.

Radiation therapy plays an integral role in the treatment of NSCLC patients across all stages of disease including early-stage, locally advanced and metastatic disease. Recent advances in treatment planning and innovative high-precision radiation delivery devices have resulted in more safe and effective radiation treatment while sparing adjacent normal tissue [10]. Being a complex therapeutic modality, radiation therapy acts by the principle mechanism of double-strand DNA helix damage that ultimately leads to cell death [11, 12]. Accordingly, DNA damage and subsequent tumor cell death have been ascribed to five basic principles known as the five "Rs" of radiation biology [13]. These include repair, repopulation, redistribution, reoxygenation, and radiosensitivity, which are critical to achieve the therapeutic goal of tumor control in radiation therapy. The most well-recognized pathway of radiation therapy-induced cellular lethality is mitotic catastrophe, in which the tumor cells are unable to complete their mitosis successfully and die in the process. At the molecular level, when tumor cells are exposed to radiation beams directly, ionization of the atoms of the tumor cells takes place, leading to the excitation of electrons. These secondary electrons directly damage the nuclear DNA of the tumor cells. The incomplete repair of these damaged DNA causes several modes of tumor cell death, such as apoptosis, necrosis, autophagy, mitotic catastrophe, or replicative senescence, all of which lead to a complex interplay between the host's immune system and the tumor microenvironment (Fig. 1) [14].

While the direct effect of radiation on cellular DNA is regarded as the primary mechanism of tumor cell death, radiation also exerts systemic antitumor effects by additional mechanisms in which the radiation stimulates the hosts' immune system and produces a phenomenon known as the "abscopal effect" (*ab scopus*, away from the target). This is also referred to as the "distant bystander effect," and implies that radiation therapy not only has a localized action on the target tumor tissue but also has an out-of-field systemic antitumor effect on distant non-irradiated tumor lesions [15].

The abscopal effect of radiation was originally described by Mole in 1953 [16] when observing that localized radiation treatment targeted at a malignant tumor triggered systemic antitumor effects resulting in the regression of patients' distant nonirradiated tumors. Unfortunately, this phenomenon was rarely observed in the clinic and was reported sporadically until relatively recently. The interest in radiation as an immunostimulatory modality began nearly five decades ago, with the first anecdotal reports of the abscopal effect in a patient with papillary adenocarcinoma [17]. Over the subsequent decades, scattered cases of the abscopal effect were reported in various malignant cancers. As novel immunotherapeutic agents began to emerge over the past decade, reports of the abscopal effect became more frequent. Concurrently, preclinical evidence of radiation therapy-induced immunogenic effects began to grow exponentially. There is now a growing consensus from the oncology community indicating that radiation therapy can exert out-of-field systemic antitumor responses through the abscopal effects in various immunogenic tumors including advanced lung cancer. The complex mechanisms by which radiation therapy induces its abscopal effects are not precisely established. However, immune-mediated cell death by radiation therapy appears to play an important role in producing the abscopal effect. Since radiation therapy modulates the tumor's immune environment, it

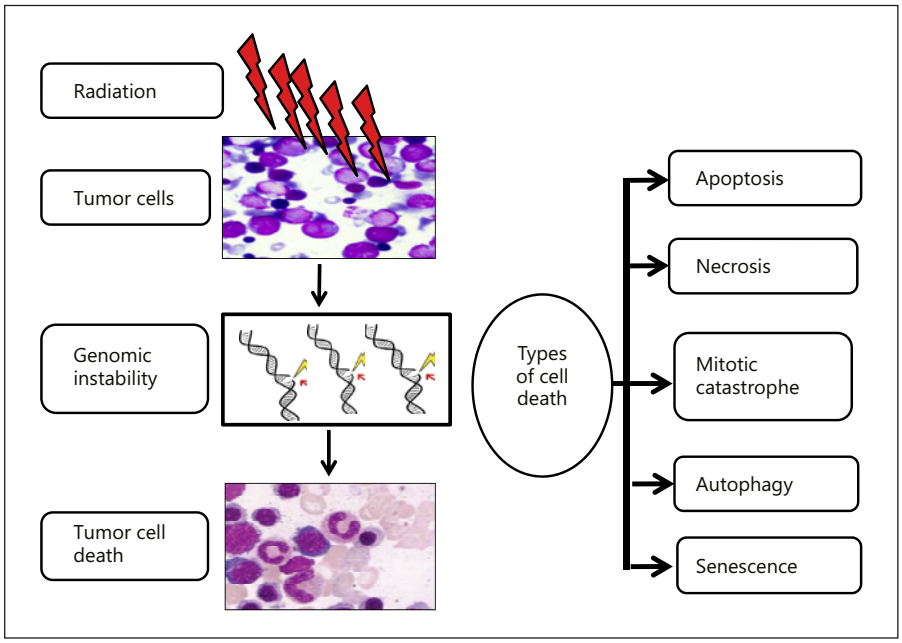

Fig. 1. Types of tumor cell death induced by radiation therapy.

is believed that radiation used in conjunction with immunotherapy may be more effective than either therapy alone in improving treatment outcomes. In fact, several recent studies have demonstrated that combining radiation with immunotherapy can boost the antitumor abscopal effect [18–21].

The proposed underlying mechanisms of the abscopal effect are based on the host's immune activation by radiation therapy. It is believed that radiation causes a tumor cell's destruction and the subsequent liberation of tumor antigens and the production of damage-associated pattern molecules, which in turn facilitates the maturation of dendritic cells, leading to differentiation of the T lymphocytes (T cells) into antitumor cytotoxic T cells through a process called immune priming [22]. During this process, a cascade of molecular events occurs, including the release of tumor antigens that act as proinflammatory mediators, stimulating monocyte production of the cytokines such as tumor necrosis factor, and interleukins leading to the upregulation of immune receptors on tumor cells [23]. The cytokines and other signaling molecules are known to alter the tumor's microenvironment and promote the influx of immune cells into lesion sites through antigen-presenting cells that specifically recognize tumor-specific antigens released by the dead cells. Through this mechanism, radiation treatment enhances tumor immunogenicity and induces the abscopal effect. Thus, the induction of an abscopal effect by radiation therapy requires a sufficient volume of T cells for the activation of the immune system, followed by adequate production and presentation of tumor-associated antigen by antigen-presenting cells to T cells, which then produce specific killer T cells for the tumor cells at primary and metastatic locations (Fig. 2) [18].

Recent advances in the understanding of the immunostimulatory 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 including advanced lung cancer. In this article, we provide an overview of the current state of knowledge and clinical experience of the abscopal effect induced by local radiation therapy either alone or in combination with immunotherapy in the treatment of advanced NSCLC.

Methods

Study Design and Search Strategy

A systematic literature search was performed to find published reports, primarily in peer-reviewed literature, using electronic databases such as MEDLINE via PubMed and Google Scholar. Combinations of the keyword "abscopal effect" with any of the following terms were used for the search in the database: "radiation therapy," "lung cancer," "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. Nonindexed journals were manually searched to find clinical evidence for radiation therapy-induced abscopal effects in patients with advanced NSCLC.

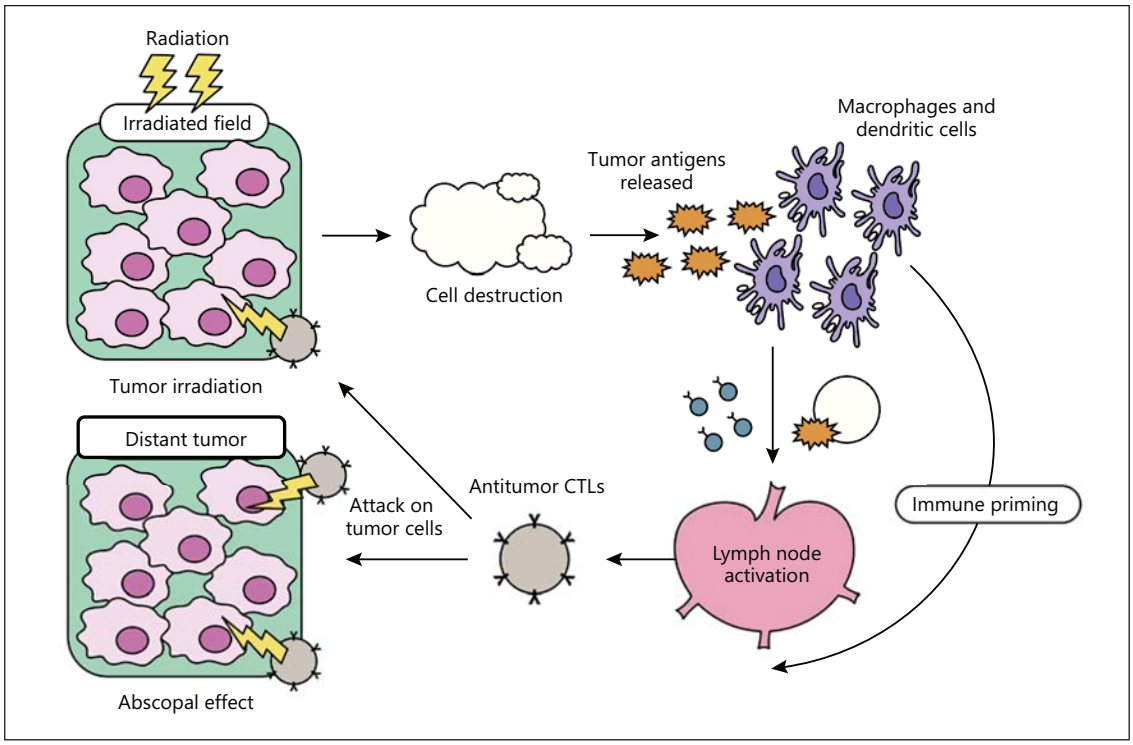

Fig. 2. Schematic drawing of the mechanism of the radiation therapy-induced abscopal effect in advanced lung cancer. Localized radiation therapy of the tumor causes cell destruction and initiation of the immune process by liberating tumor antigens and producing damage-associated molecules, which lead to the maturation of dendritic cells and improved priming and activation of effector cytotoxic T lymphocytes (CTLs). The tumor antigens also act as proinflammatory 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 CTLs facilitate tumor cell elimination not only by attacking the tumor bulk in the irradiated area but also by traveling to metastatic sites and promote tumor regression or elimination, a process known as the abscopal effect.

Clinical Evidence of Abscopal Effects

Clinical evidence of radiation-induced abscopal effects in advanced NSCLC has been reported for the past three decades. However, most of the clinical evidence exists in the form of case reports (Table 1) and small nonrandomized studies (Table 2).

Case Reports Showing the Abscopal Effect

A recent study by Garelli et al. [24] reported the ability of locally administered radiation therapy to induce abscopal effects in the cases of 3 patients with lung cancer. In the first case, a 54-year-old male patient had a large cell pulmonary neuroendocrine carcinoma of the right upper lobe with bilateral adrenal metastases. The patient was initially administered 4 cycles of chemotherapy (pemetrexed, cisplatin, and bevacizumab), but his disease soon progressed in the right upper lobe as well as in both of the adrenal glands. The patient had a failed second-line therapy with nivolumab after chemotherapy, but subsequently he developed symptomatic spinal cord compression due to tumor invasion. Following a hemilaminectomy of the 3rd thoracic vertebra combined with a resection of the epidural tumor mass, the patient underwent radiation therapy (30 Gy in 10 fractions) targeting the 2nd and 3rd thoracic vertebrae while continuing immunotherapy with nivolumab. At the evaluation 4 months after his postoperative radiotherapy, the patient experienced a partial regression of the lung tumor and adrenal metastases, suggesting an abscopal effect of radiation therapy.

The second case involved a 64-year-old male patient with a central adenocarcinoma of the left upper lobe metastasized to the brain and ocular system. Initial chemotherapy treatment consisted of 4 cycles of nab-paclitaxel/carboplatin with atezolizumab followed by 4 cycles of atezolizumab, which alone resulted in an excellent response of the ocular metastasis, but the patient progressed with brain metastasis. A partial remission was

Table 1. Summary of clinical case reports of the abscopal effect of radiation therapy in advanced NSCLC

Patient		Is primary tumor treated?	Location of RT	Total RT dose, Gy	Each radiation therapy dose and fractions	IT agent	Site with abscopal effect	Time to abscopal response	Study [Ref.], year
gender	age, years								
Male	54	No	Thoracic vertebrae	30	3 Gy, 10 fractions	NIV	Adrenal glands and lung lesions	4 months	Garelli et al. [24], 2019
Male	64	No	Brain lesions	30	3 Gy, 10 fractions	ATE	Lung and mediastinal lymph nodes	4 months	Garelli et al. [24], 2019
Male	70	No	Brain lesions	30	3 Gy, 10 fractions	PEM	Lung and pleural disease	After RT	Garelli et al. [24], 2019
Female	62	Yes	Lung	27	3 Gy, 9 fractions	NIV	Adrenal mass	6 months	Bitran [25], 2019
Male	70	Yes	Lung	48	12 Gy, 4 fractions	None	Liver metastases	3 months	Kim and Kim [26], 2019
Male	71	No	Brain lesions	48	6 Gy, 8 fractions	ATE	Nodules in the basal segment of the right lower lung	3 months	Lin et al. [27], 2019
Female	76	No	Mediastinum	60	2 Gy, 30 fractions	None	Lymph node metastases Pulmonary metastases	3 weeks 3 months	Kuroda et al. [28], 2019
Male	63	No	Right hip joint	30	NS	NIV	Various metastatic lesions	6 weeks	Yaguchi et al. [29], 2019
Male	47	No	Brain lesions	25	5 Gy, 5 fractions	None	Lung tumor	3 months	Hamilton et al. [30], 2018
Male	47	No	Lymph nodes	18	3 Gy, 6 fractions	NIV	Nonirradiated lymph node	2.5 months	Britschgi et al. [31], 2018
Female	64	Yes	Paramediastinal mass	37.5	7.5 Gy, 5 fractions	Dendritic cell	Pulmonary metastases	10 months	Cong et al. [32], 2017
Male	63	No	Brain lesions	45	3 Gy, 15 fractions	None	Lung and mediastinal lymph nodes	9 months	Katayama et al. [33], 2017
Female	67	No	Calvarial metastasis	30	3 Gy, 10 fractions	None	Skin nodules	1 month	Cummings et al. [34], 2017
Male	60	No	Liver lesions	40	2 Gy, 20 fractions	NIV	Nonirradiated primary tumor and other metastases	3 weeks	Komatsu et al. [35], 2017
Male	64	No	Liver lesions	30	6 Gy, 5 fractions	IPI	Various metastases	3 months	Golden et al. [36], 2013
Female	78	Yes	Lung	60	2 Gy, 30 fractions	None	Outside of the radiation field	2 months	Siva et al. [37], 2013
Male	74	No	Lymph nodes	48	2 Gy, 24 fractions	BCG-CWS	Pulmonary metastases	6 months	Kodama et al. [38], 2014
Male	72	Yes	Lung	47.6	1.7 Gy, 28 fractions	GM-CSF	Various metastases	NR	Yoon and Lee [39], 2012
Male	NS	Yes	Lung	35	3.5 Gy, 10 fractions	None	Subcutaneous metastases	During treatment	Rees and Ross [40], 1983

ATE, atezolizumab; BCG-CWS, bacillus Calmette-Guérin cell wall skeleton; GM-CSF, granulocyte-macrophage colony-stimulating factor; IPI, ipilimumab; IT, immunotherapy; NIV, nivolumab; NR, not reported; NS, not specified; NSCLC, non-small cell lung cancer; PEM, pembrolizumab; RT, radiation therapy.

Table 2. Summary of cohort study reports of the abscopal effect of radiation therapy in advanced NSCLC

Study type	Patients, *n*	Radiation therapy	Radiation therapy location	Total radiation therapy dose and fractions	Immunotherapy agent	Abscopal response, *n* (%)	Study [Ref.], year
Prospective	6	SRT	Various lesions	25–48 Gy, 3–4 fractions	Nivolumab	4 (67)	Miyamoto et al. [41], 2019
Prospective	39	Not specified	Not specified	30 Gy, 3–5 fractions	Ipilimumab	12 (31)	Formenti et al. [44], 2018
Retrospective	7	HFRT/SBRT/SRS	Various lesions	Not specified	Pembrolizumab or nivolumab	3 (43)	Trommer et al. [42], 2019
Prospective	16	Not specified	Various lesions	Not specified	GM-CSF	2 (13)	Liu et al. [43], 2019

GM-CSF, granulocyte-macrophage colony-stimulating factor; HFRT, hypofractionated radiation therapy; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiation therapy.

also observed in the thoracic tumor manifestations. However, no further shrinkage of these lesions was seen after 4 additional cycles of atezolizumab monotherapy. At that point, the patient received whole-brain radiation therapy (WBRT; 30 Gy in 10 fractions) while continuing immunotherapy with atezolizumab. At the follow-up evaluation 4 months after WBRT, the patient not only experienced a partial regression of his brain lesions, but also had complete remission of his lung and mediastinal tumor masses, indicating an abscopal effect of radiation therapy.

The third case involved a 70-year-old male patient who had a central adenocarcinoma of the middle lobe with positive mediastinal lymph nodes and a malignant ipsilateral pleural effusion. Because of PD-L1 tumor positivity, the patient received immunotherapy with pembrolizumab, leading to a partial response. A year after his immunotherapy treatment, the patient developed pleural disease and progressed with a clinically symptomatic brain metastasis. The patient later received WBRT (30 Gy in 10 fractions) while continuing immunotherapy with pembrolizumab. A follow-up evaluation after radiation therapy showed partial regression of the lung tumor and pleural effusion, suggesting an abscopal effect of radiation therapy.

In another recent study, Bitran [25] reported a case of an abscopal response in a metastatic lung cancer patient after local radiation therapy. This case involved a 62-year-old female patient who presented with a stage IV adenocarcinoma of the left lung with a large metastatic left adrenal lesion. The patient initially received 2 cycles of chemotherapy with carboplatin and pemetrexed, but her disease progressed. In an attempt to better control her lung disease, she received palliative radiation therapy to a total dose of 27 Gy delivered to the left lower lobe lung mass in 9 fractions followed by immunotherapy with nivolumab. An evaluation 4 months after radiation therapy showed significant regression of her adrenal tumor mass (reduced to 2.2 cm from 10.0 cm), indicating an abscopal effect of radiation therapy.

In another, more recent study, Kim and Kim [26] described the abscopal response in a liver metastasis in a patient with a primary NSCLC. In this case, a 70-year-old male patient presented with an unresectable cholangiocarcinoma (bile duct cancer) at diagnosis. The patient received 8 cycles of palliative-intent chemotherapy with cisplatin and gemcitabine. Although his lung mass remained stable, the patient progressed with liver metastasis. The patient was then treated with stereotactic body radiation therapy to a dose of 48 Gy delivered in 4 fractions to the right upper lobe NSCLC. At the evaluation 3 months after his radiation therapy, the patient showed spontaneous and complete regression of his liver metastatic lesions, revealing an abscopal effect of radiation therapy.

Lin et al. [27] reported a case of an abscopal effect after stereotactic brain radiation therapy as second-line treatment in a patient with lung adenocarcinoma. In this case study, a 71-year-old male patient was diagnosed with a poorly differentiated stage IV adenocarcinoma in the right lobe of the lung. The patient was initially administered 6 cycles of chemotherapy with nedaplatin and paclitaxel, but the primary tumor became enlarged, indicating failure of his first-line chemotherapy. The introduction of immunotherapy with atezolizumab resulted in a reduction of the primary tumor and mediastinal lymph nodes. However, the patient subsequently progressed with metastasis in his right parietal lobe of the brain. The

patient then underwent stereotactic X-Knife radiation to his brain lesion to a total dose of 48 Gy in 8 fractions while continuing his immunotherapy with atezolizumab. At the follow-up evaluation 3 months after his radiation to the brain, the patient experienced a reduction in the nodules in the basal segment of his right lower lung. In addition, the number of subpleural lesions in the basal segment of the left lower lung, as well as multiple lymph nodes in the mediastinum, had reduced in size. These findings suggest that brain radiation therapy can induce an extracranial abscopal response in patients with metastatic lung cancer.

Kuroda et al. [28] reported a case of an abscopal effect of radiation therapy in the case of a 76-year-old female patient who was diagnosed with biopsy-proven stage IIIA pulmonary adenocarcinoma. Initially, her disease was managed by watchful observation without any treatment, but 2 years later, the patient progressed with multiple mediastinal and right hilar lymph node metastases. Subsequently, the patient received radiation therapy to a total dose of 60 Gy delivered in 30 fractions to her chest lesions over a period of 6 weeks. The radiation therapy targeted her multiple mediastinal lymph node metastases but spared the spinal cord and hilum of the left lung. A chest CT scan 6 weeks after her radiation therapy showed a reduction of the lymph node metastases. However, the patient developed new metastatic lesions in her left hilar and right supraclavicular lymph nodes and in the pulmonary nodules outside of the radiation field. A follow-up chest CT scan 12 weeks after the completion of her radiation therapy to the mediastinum revealed a complete disappearance of her multiple pulmonary metastases, indicating an abscopal effect of radiation therapy.

Yaguchi et al. [29] reported a case of an abscopal effect of radiation therapy in a patient with metastatic pulmonary pleomorphic carcinoma. In this case study, a 63-year-old male initially presented with an abnormal shadow in his lung. The findings from the bronchoscopy and imaging were consistent with the diagnosis of a stage IIIA adenocarcinoma in the right lower lobe of the lung. The patient soon underwent surgical resection of the right lower lobe and lymph node dissection via thoracotomy. However, the patient immediately progressed with rapid systemic metastatic disease. The patient then received first-line chemotherapy with paclitaxel and carboplatin and palliative bone radiation therapy to a total dose of 30 Gy to his right hip joint of the right femur. Because of his disease progression, the patient was switched to immunotherapy with nivolumab after 1 cycle of chemotherapy. Within 6 weeks following immunotherapy, the patient achieved a marked tumor regression and a near-complete response, suggesting that the efficacy of immunotherapy may have been boosted by a radiation therapy-induced abscopal effect.

Hamilton et al. [30] reported a case of an abscopal effect after radiosurgery for a solitary brain metastasis in a patient with advanced NSCLC. This case involved a 47-year-old male patient who initially presented with right groin and lower-extremity numbness and had an unremarkable review of other systems. His past medical history included an aorto-occlusive disease status post femoral-popliteal bypass, peripheral artery disease, coronary artery disease, and tobacco dependence. Based on the presence of the aortofemoral bypass graft occlusion, the patient was diagnosed with right limb occlusion with critical limb ischemia of the right lower extremity. CT angiography of his chest initially indicated the presence of a nodule at the left lung apex, slightly cavitary in nature, together with a left paratracheal soft tissue density. Two months prior to the recommended follow-up visit, the patient was admitted to the emergency room with bilateral chest pain and associated shortness of breath and dyspnea. An evaluation using CT angiography revealed an increase in the left upper lobe mass density and bilateral hilar adenopathy, indicating a primary neoplasm with metastatic disease. Furthermore, the patient's biopsy confirmed a poorly differentiated NSCLC. Oncologic positron emission tomography (PET) imaging showed an invasion of the pleura with perivascular and lymphatic metastatic involvement, confirming a hypermetabolic left upper lung lobe mass. Magnetic resonance imaging (MRI) of the brain revealed a metastatic lesion in the left frontal lobe with surrounding edema. The patient later underwent brain radiosurgery to a total peripheral dose of 25 Gy delivered in 5 fractions to the solitary brain lesion. The patient did not receive any form of systemic therapy, such as chemotherapy or immunotherapy. A follow-up assessment using brain MRI 1 month after radiotherapy initiation revealed that the metastatic lesion size in the brain was reduced considerably. Further follow-up evaluations 3 and 7 months after brain radiation therapy showed complete resolution of the original left upper lobe pleural-based mass, indicating an abscopal response to radiation therapy.

Britschgi et al. [31] described a case of an abscopal effect of radiation therapy in a patient with metastatic NSCLC. In this case, a 47-year-old male patient was initially diagnosed with a stage IIIB lung adenocarcinoma. As part of a clinical trial, the patient was initially treated with chemotherapy and cetuximab, followed by radiation

therapy with cetuximab and surgical resection of the primary tumor. Although the patient achieved a pathologically complete response, a retroperitoneal lymph node relapse occurred 8 weeks after his surgery. The patient later underwent palliative chemotherapy with cisplatin/pemetrexed, followed by pemetrexed maintenance. However, the patient not only developed serious hematological adverse effects, but also progressed with abdominal lymph node disease. Later, the patient was treated with anti-PD-1 (programmed death 1) immunotherapy with nivolumab after being enrolled in an expanded access program. The nivolumab therapy resulted in a mixed response with regression of the initial tumor sites and progression of 3 new abdominal lymph node metastases. At this point, the patient received stereotactic body radiation therapy to a dose of 18 Gy in 6 fractions to 2 of the 3 metastatic lymph node lesions while continuing his immunotherapy. Because of its close proximity to the small bowel, the third lymph node lesion was not treated with stereotactic radiation therapy (SRT). This nonirradiated third lymph node lesion served as a reference lesion for immunotherapy response. A PET/CT imaging evaluation 10 weeks after his radiation therapy indicated that the patient had achieved a complete radiological and metabolic response not only in the radiated lymph node metastatic lesions but also in his nonirradiated lesion of the third lymph node, revealing an abscopal response to his treatment.

A case study by Cong et al. [32] has shown in a patient with metastatic NSCLC that radiation therapy can induce an abscopal response. This case involved a 64-year-old male patient who presented with a right-sided chest wall mass with concurrent pain. Excision of his chest wall mass revealed a metastatic adenosquamous carcinoma. After failure of first-line chemotherapy with cisplatin and pemetrexed, the patient received immunotherapy with first dendritic cells and cytokine-induced killers (DC-CIK) combined with gefitinib therapy. However, the patient progressed with marked tumor growth in the lung. Thereafter, the patient received third-line systemic treatment with pemetrexed combined with gefitinib and continued the second-line DC-CIK immunotherapy. However, the patient developed progressive symptomatic cough and could not tolerate the chemotherapy. He then received stereotactic ablative body radiation therapy (SABR) to a dose of 37.5 Gy in 5 daily fractions to the paramediastinal tumor foci. A follow-up chest evaluation performed 10 months after completion of SABR showed complete regression of his pulmonary lesions, suggesting an abscopal effect of radiation therapy.

Katayama et al. [33] reported abscopal effects of radiation therapy in a patient with metastatic NSCLC. This case study included a 63-year-old male patient who had presented with worsening dysgraphia and memory impairment. A chest CT scan showed a 4.0-cm solitary tumor in the upper lobe of the left lung with mediastinal lymphadenopathy. A brain MRI revealed a 3.0-cm solitary tumor, assumed to be a metastatic lesion, with cerebral edema extending from the left temporal lobe to the occipital lobe. The lung bronchoscopic cytology and biopsy indicated malignant cells that were consistent with NSCLC. Subsequently, the patient was diagnosed with stage IV NSCLC. As part of the initial treatment, the patient underwent enucleation of the brain tumor because of his rapidly progressive symptoms. A pathological examination of the excised cranial lesion confirmed it to be an NSCLC metastasis. Although tumor-infiltrating lymphocytes were not observed extensively, his brain metastasis progressed immediately after the surgery, and the patient received WBRT plus a boost of radiotherapy to a total dose of 45 Gy delivered in 15 fractions. In addition, he underwent palliative radiation (30 Gy in 10 fractions) to a 3rd lumbar spine vertebral metastasis. At the follow-up evaluation 7.0 weeks after WBRT, the tumor in the left upper lobe of the lung and his mediastinal lymph nodes had regressed in size. Furthermore, the lung tumor had also shrunk significantly, suggesting abscopal responses to radiation therapy without any systemic treatment.

Cummings et al. [34] reported a case of an abscopal effect of radiation therapy in a patient with an atypical neuroendocrine carcinoid lung cancer. In this case study, a 67-year-old female patient presented with a tender subcutaneous mass measuring 1.5 cm in her right neck. A punch biopsy of the mass and immunohistochemical evaluation suggested an intermediate-grade bronchial neuroendocrine carcinoma. A year later, the patient was enrolled in a clinical trial of temozolomide and an oral poly (ADP-ribose) polymerase (PARP) inhibitor. After 4.0 months on the treatment, she discontinued the trial due to disease progression. The patient later underwent palliative radiation therapy to a total dose of 30 Gy delivered in 10 fractions targeted to a symptomatic calvarial metastasis. A follow-up evaluation 1.0 month after the palliative skull radiation revealed a rapid improvement in her skin nodules, suggesting an abscopal effect of radiation therapy. The patient had a durable complete response to radiation therapy even after 18 months had passed.

Komatsu et al. [35] described a case of an abscopal response in a lung cancer patient who progressed on im-

munotherapy with nivolumab. In this case, a 60-year-old male patient was diagnosed with an advanced lung adenocarcinoma. Following neoadjuvant chemoradiotherapy, the patient underwent 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. However, 6 months after his lobectomy, the patient developed a solitary liver metastasis and intrapulmonary metastasis. The patient was then administered chemotherapy with 1 course of cisplatin and pemetrexed, but his disease progressed. The patient later received immunotherapy with nivolumab. However, the patient's disease continued to progress with the development of liver metastasis. At this point, the patient received radiation therapy to a dose of 40 Gy in 20 fractions to the liver metastatic lesions. A follow-up evaluation 3 weeks after the completion of his liver radiation therapy, the patient showed a remarkable reduction not only in the tumor's size, but also in the intrapulmonary metastatic lesions that were away from the radiation field, indicating an abscopal response to radiation therapy.

Golden et al. [36] reported a case of an abscopal effect in a patient with metastatic NSCLC following radiation therapy. This case involved a 64-year-old male patient who had a previous history of smoking and presented with a palpable left supraclavicular nodule. Pathology of his mass using immunohistochemistry staining revealed a metastatic adenocarcinoma. A subsequent PET/CT imaging scan showed 2 right upper lobe nodules, 1 left lower lobe nodule, and 1 right supraclavicular and bilateral hilar/mediastinal adenopathy, indicating stage IV NSCLC. Although the patient initially responded to chemotherapy with pemetrexed and carboplatin followed by pemetrexed maintenance therapy, a year later he developed new hypermetabolic liver lesions, new periaortic adenopathy, and a new bony lesion in his sacrum. The patient then received gemcitabine/vinorelbine therapy, but soon progressed with liver lesions and growth of new lytic lesions in his bony pelvis, thoracolumbar spine, and right humerus. The progressive bone metastases and liver lesions were treated with radiation to a total dose of 30 Gy delivered in 5 fractions with concurrent ipilimumab. At the follow-up evaluation 3.0 months after his treatment, the patient had achieved a dramatic treatment response in both the irradiated and the nonirradiated distant tumor lesions, revealing an abscopal effect of radiation therapy.

Siva et al. [37] described an instance of an abscopal effect induced by radiation therapy in a patient with metastatic NSCLC. In this case, a 78-year-old female patient was diagnosed with a biopsy-proven, bulky, left-sided primary lung adenocarcinoma. The patient initially underwent concurrent chemoradiation therapy. Although a complete metabolic response was seen after the chemoradiation therapy, the patient subsequently progressed with adrenal and bone metastases. As part of a prospective clinical trial, the patient, subsequently, received a single fraction of 26-Gy SABR to the primary tumor. A follow-up evaluation 1 year after the completion of her radiation therapy showed a complete metabolic response in both the irradiated and the nonirradiated sites, indicating an abscopal effect of radiation therapy.

Kodama et al. [38] described a case of an abscopal effect of radiation therapy in a patient with lung adenocarcinoma. In this case, a 74-year-old male patient was diagnosed with a biopsy-proven stage IIA adenocarcinoma. Initially, the patient was under watchful observation with no treatment, but 23 months later, he progressed with metastatic disease involving lymph nodes and multiple pulmonary nodules. Radiation therapy was administered to a total dose of 30 Gy delivered in 24 fractions to his supraclavicular lymph node metastases and a 10-Gy boost to the nodular lesion followed by innate immunotherapy using the cell wall skeleton of *Mycobacterium bovis* bacillus Calmette-Guérin. At the follow-up 3 months after his treatment, the patient showed complete regression of all his metastatic tumor lesions, indicating an abscopal effect of radiation therapy. Yoon and Lee [39] reported a case of an abscopal effect of radiation therapy in a patient with metastatic NSCLC. This case involved a 72-year-old male patient who was diagnosed with unclassifiable stage IIIB metastatic NSCLC. The patient underwent fractional radiation therapy to a total dose of 47.6 Gy delivered in 28 daily fractions of 5 treatments per week. In addition, the patient received treatment with modulated electrohyperthermia (oncothermia) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Following completion of his radiation treatment, the patient experienced a nearly complete remission in the multiple metastatic lymph nodes, which were distantly away from his radiotherapy field. The outcomes from this case study suggest a successful abscopal effect with local radiation therapy in combination with oncothermia and GM-CSF immunostimulation.

Rees and Ross [40] reported a case of an abscopal effect in a patient with metastatic NSCLC following radiation therapy. This case involved a patient who was diagnosed with metastatic adenocarcinoma of the lung. Using parallel-opposed beams, the patient was administered radiation therapy to a total dose of 35 Gy delivered in 10 frac-

tions to the mediastinum and left lower lung. While receiving radiation treatment, regression of the nonirradiated tumor was seen in the patient's subcutaneous metastases in his forehead and in his left shoulder. Furthermore, at the follow-up evaluation 2 weeks after his radiation therapy, regression in the subcutaneous nodules was seen, suggesting an abscopal effect of radiation therapy.

Cohort Studies Showing an Abscopal Effect

A recent feasibility study by Miyamoto et al. [41] assessed the safety and efficacy of nivolumab administration after SRT in chemotherapy-pretreated patients with advanced/recurrent NSCLC. The study included 6 chemotherapy-pretreated patients with advanced/recurrent NSCLC. Of the 6 patients, 4 had second-line therapy and the other 2 underwent third-line therapy prior to the study enrollment. Five of the 6 patients received SRT (25–48 Gy in 4–5 fractions) to their primary lesions. The sixth patient had previously undergone concurrent chemoradiotherapy and, therefore, received SRT to the cervical lymph nodes. All patients received nivolumab within 2 weeks of the first fraction of SRT. Four of the 6 patients had measurable lesions outside their irradiated area. Post-treatment evaluation showed 1 complete response and 2 partial responses. Three of the 5 patients who initially had measurable lesions outside the irradiated field responded to the treatment, demonstrating an abscopal effect of the radiation therapy.

In a recent retrospective study, Trommer et al. [42] evaluated the abscopal effect in metastasized cancer patients who received radiation therapy and pembrolizumab or nivolumab concurrently. The study included 24 patients with various metastasized tumors (NSCLC, $n = 7$; melanoma, $n = 14$; renal, $n = 3$; and head and neck, $n = 1$). Of the 24 patients, 7 had lesion shrinkage outside their radiation therapy field, indicating an abscopal effect of radiation therapy. Among the 7 patients who achieved an abscopal response, 3 were diagnosed with melanoma, 3 with NSCLC, and 1 with renal cell carcinoma.

Liu et al. [43] assessed the abscopal effects of local radiation therapy in combination with GM-CSF in patients with metastatic thoracic cancers. In this study, 30 patients with metastatic thoracic cancers were included. Of the 30 patients evaluated, 16 patients had metastatic lung cancer. All patients included in the study received local radiation therapy in combination with GM-CSF. Post-treatment evaluation revealed that 2 of the 16 patients achieved a partial response, with the regression of their tumors outside the irradiated field indicating an abscopal effect of radiation therapy. In addition, 5 patients with metastatic lung cancer achieved stable disease with the combination therapy.

A prospective clinical trial (NCT02221739) by Formenti et al. [44] evaluated the abscopal effect of palliative radiation therapy to a single metastatic lesion in patients with metastatic NSCLC. Specifically, the trial examined the efficacy of radiation therapy in inducing abscopal responses in chemotherapy-refractory metastatic NSCLC patients who had failed to respond to ipilimumab alone or in combination with chemotherapy. The trial included 39 metastatic NSCLC patients who underwent palliative radiation therapy to a total dose of 30 Gy in 5 fractions or 27 Gy in 3 fractions and concurrent ipilimumab. Post-treatment evaluation showed an objective radiographic response rate of 18% (7 of 39 patients) and a disease control rate of 31% (7 of 39 patients). Thus, the study findings indicated that palliative radiation therapy to a single metastatic lesion resulted in the regression of not only the irradiated lesions but also the nonirradiated lesions, demonstrating an abscopal effect of the radiation therapy. Furthermore, palliative radiation therapy increased serum interferon-β, early dynamic changes in blood T-cell clones, and rapid in vivo expansion of CD8 T cells, supporting that the abscopal response is a radiation-induced stimulation of the immune system.

Radiation Dose and Induction of the Abscopal Effect

Over the past few decades, numerous case reports have been published on the sporadic abscopal effect events in patients with various tumor types including lung, melanoma, renal cell, breast, bladder, colorectal, and other tumors (for a detailed review, see D'Andrea and Reddy [12]). A careful analysis of those previously reported case studies indicates that abscopal responses can be seen regardless of the radiation dose per fraction. Specifically, in those case studies, the radiation dose ranged from 1.0 to 18.0 Gy per fraction, and the earliest abscopal effect was seen soon after the completion of radiation therapy [12]. Similarly, a review by Abuodeh et al. [45] that included 46 cases with various tumor types such as NSCLC noted abscopal responses to radiation therapy alone (except for 5 patients, who had immunotherapy during treatment) at various doses ranging from 1.5 to 26 Gy per fraction. The review of NSCLC cases in this study also indicates that abscopal effects can be seen with the radiation dose fraction ranging from 1.7 to 12 Gy. Collectively, these findings suggest that the abscopal effects that occur do so in-

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

ClinicalTrials.gov identifier	Study phase	Radiation therapy	Total radiation therapy dose and fractions	Immunomodulator	Endpoint	Location
NCT03176173	Phase II	IGRT	NS	Nivolumab, or pembrolizumab or atezolizumab	To assess the abscopal response rate of IGRT in combination with immunotherapy	USA
NCT02831933	Phase II	SBRT	30 Gy (6 Gy in 5 fractions)	Nivolumab	To assess the abscopal effect of SBRT in combination with ADV/HSV-tk plus valacyclovir therapy	USA
NCT02976740	Phase II	SBRT	50 Gy (5 Gy in 10 fractions)	rhGM-CSF	To assess the abscopal response rate of radiation therapy with rhGM-CSF	China
NCT02787447	Phase II	HFRT	45 Gy (3 Gy in 15 fractions)	Thymosin	To assess the proportion of patients with an abscopal response assessed at 1–6 months after the radiation therapy	China
NCT02542930	Phase II	NS	35 Gy (3.5 Gy in 10 fractions)	Thymalfasin	To assess the proportion of patients with an abscopal response assessed at 7–8 weeks after the initiation of treatment	China
NCT03113851	Phase II	NS	35 Gy (3.5 Gy in 10 fractions)	rhGM-CSF	To assess the abscopal response rate of radiation therapy with rhGM-CSF	China
NCT04238169	Phase II	SBRT	30–50 Gy (10 Gy in 3–5 fractions)	Toripalimab	To assess the efficacy of the abscopal effect induced by SBRT and immunotherapy in advanced NSCLC	China
NCT03474497	Phase I/II	NS	24 Gy (3 Gy in 8 fractions)	Pembrolizumab	To determine the abscopal response rate	USA
NCT03509584	Phase I	HFRT	24 Gy (3 Gy in 8 fractions)	Nivolumab with or without ipilimumab	To assess the abscopal response rate to radiation therapy in combination with immunotherapy	France
NCT02858869	Phase I	SRS	18–21 Gy (1 Gy in 18–21 fractions)	Pembrolizumab	To evaluate treatment response at nonirradiated and extracranial sites (i.e., the abscopal effect)	USA

HFRT, hypofractionated radiation therapy; IGRT, image-guided radiation therapy; NS, not specified; NSCLC, non-small cell lung cancer; rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; RT, radiation therapy; SRS, stereotactic radiosurgery; SBRT, stereotactic body radiation therapy.

dependently of the radiation dose, fractionation, modality, and the characteristics of the target lesion.

The primary intention of radiation therapy is to deliver a calculated quantum of tumoricidal radiation dose to the targeted tumor while limiting damage to the surrounding normal tissues. Traditionally, radiation therapy is delivered in smaller daily doses typically ranging from 1.8 to 2.0 Gy per fraction for a total radiation dose of 50–80 Gy [46]. However, recent technological advances in planning and delivery of external beam radiation have allowed conformal delivery of larger doses (8–20 Gy) per fraction while minimizing the dose to the normal tissues with higher precision. The larger doses of radiation per fraction can induce cancer cell death in a manner that is DNA damage independent and can produce systemic antitumor effects [46]. Although it is yet to be established clinically, preclinical evidence indicates that hypofractionated radiation may be more effective in certain tumor types than conventionally fractionated (2-Gy) doses in inducing an abscopal effect when combined with immunotherapy using cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibition [47].

Due to the rarity of this phenomenon, currently many strategies are being explored to increase the prevalence of abscopal effects. These strategies were based on the combination of radiation therapy with novel immunotherapy agents that stimulate dendritic cells to aggravate tumor antigen-presenting vaccination with autologous tumor cells, targeting toll-like receptors [48, 49]. In addition, these strategies also exploit the combination of these two modalities using different approaches such as timing and sequential or concurrent therapies in relation to the induction of abscopal effects in patients with metastatic tumors including NSCLC [12]. Currently, many investiga-

tions have focused on evaluating abscopal effects using varying doses and fractionations of radiation therapy in combination with immunotherapy. It should be noted that the radiation dose and fractionation regimen optimized for a robust local tumor response might be different from that optimized for a distant abscopal response. Nevertheless, additional studies are needed to evaluate tumor-specific thresholds for the induction of abscopal effects.

Ongoing Clinical Trials Evaluating the Abscopal Effect of Radiation Therapy

During the past decade, the number of case reports and small studies that have evidenced an abscopal effect after the use of radiation therapy in patients with advanced cancers including lung cancer has increased dramatically. Moreover, the abscopal effects induced by radiation therapy can be augmented with the addition of immunotherapy. The optimal ways to integrate the combination of radiation therapy and immunotherapy, particularly with respect to dose, fractionation, and sequencing, or the concurrent use of these modalities are being investigated in phase I–II trials of advanced cancers including lung cancer (Table 3). These clinical trials have the potential to unleash the power of radiation therapy-induced abscopal effects that can eradicate malignant tumor cells and could represent a great leap forward in our knowledge of the treatment of not only primary tumors but also various tumor types of metastatic cancers including lung cancer. Moreover, the available clinical evidence, together with the findings from ongoing work in this promising field, provides investigators with a solid platform of data to explore and build on for treatment options for various metastasized cancers. These ongoing trials for advanced cancers may set a new stage for the critical role of radiation therapy, whereas this modality was in the past traditionally reserved for only local or palliative therapy.

Conclusions and Future Perspectives

In the past, the mechanism of localized radiation therapy has been based on five principles (the 5 Rs): repair, repopulation, redistribution, reoxygenation, and radiosensitivity [13]. Currently, the immunogenic effect of radiation therapy is established based on its antitumor effects on nonirradiated tumor sites through the phenomenon known as the abscopal effect. The abscopal effect of radiation therapy is mediated by multiple different mechanisms involved in the tumor microenvironment. However, abscopal effects were noted to be relatively rare when radiation therapy was used alone; the addition of immunotherapy to radiation therapy boosts the abscopal response through therapeutic synergy. The combined use of radiation therapy with immunotherapy, especially with checkpoint inhibitors, has shown an increased synergy as radiation therapy can recruit näive T cells to the antitumor immune response, while anti-PD-1 therapy can reinvigorate already primed, but exhausted, tumor-specific T cells [50].

Although radiation therapy alone can induce immune responses through the liberation of tumor antigens that activate the immune system, its optimal partnership with immunotherapy agents remains to be explored in order to best maximize the synergistic effects of this combined therapy. The development of biomarkers to predict the response to combination therapy can help in identifying those patients who would most likely benefit from such a therapy. Currently, a number of trials evaluating the clinical efficacy of radiation therapy in combination with immunotherapy in advanced NSCLC and other cancers are underway. Early findings from some of these studies suggest the potential synergistic relationship of these combinations. However, the findings from these ongoing and planned clinical trials will help better define how to optimize and use the combination of these two unique modalities in the treatment of advanced NSCLC and other cancers.

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Statement of Ethics

This is a review article and is exempt from ethics committee approval.

Conflict of Interest Statement

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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Author Contributions

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

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