Received: 11 July 2022 | Accepted: 29 December 2022

DOI: 10.1002/cai2.53

REVIEW

CANCER INNOVATION

Radiotherapy, photodynamic therapy, and cryoablation-induced abscopal effect: Challenges and future prospects

Sadik Ali Mohammad | **Arshadul Hak** | **Sunil V. Pogu** | **Aravind K. Rengan**

Indian Institute of Technology Hyderabad, Kandi, Sangareddy, Telangana, India

Correspondence
Aravind K. Rengan, Indian Institute of Technology Hyderabad, Kandi, Sangareddy, Telangana 502284, India.
Email: aravind@bme.iith.ac.in

Funding information
Impacting Research Innovation and Technology, Grant/Award Numbers: 4291, 00275; Council of Scientific and Industrial Research (CSIR), Grant/Award Number: 09/1001(0092)/2021-EMR-I.; DBT India, Grant/Award Number: DBT/2020/IIT-H/1336; Department of Science and Technology, Ministry of Science and Technology, India, Grant/Award Number: INSPIRE/04/2015/00037

Abstract

Local therapy modalities such as radiation therapy, photodynamic therapy, photothermal therapy, and cryoablation have been used to treat localized tumors for decades. The discovery of the abscopal effect causes a paradigm shift where local therapy also causes systemic effects and leads to the remission of nonirradiated tumors. The abscopal effect of radiation therapy, alone or in combination with other treatments, has been extensively studied over the last six decades. However, the results are unsatisfactory in producing robust, reproducible, and long-lasting systemic effects. Although immunotherapy and radiation therapy are promising in producing the abscopal effect, the abscopal effect's mechanism is still unclear, owing to various factors such as irradiation type and dose and cancer type. This article reviews the research progress, clinical and preclinical evidence of the abscopal effect by various local therapies alone and in combination with chemotherapy and immunotherapy, case reports, and the current challenges in producing the abscopal effect by various local therapies, focusing on radiotherapy, photodynamic therapy, cryoablation, and the prospects for obtaining a robust, reproducible, and long-lasting abscopal effect.

KEYWORDS
abscopal effect, local therapy, radiotherapy, photodynamic therapy, cryoablation, immunotherapy, cancer

Abbreviations: APC, antigen-presenting cell; CRT, calreticulin; CTL, cytotoxic T lymphocytes; CTLA4, cytotoxic T lymphocyte-associated antigen 4; DAMPs, damage-associated molecular patterns; EBRT, external beam radiation therapy; HMGB1, high-mobility group box 1 protein; ICD, immunogenic cell death; IMRT, intensity-mediated radiation therapy; NSLC, non-small cell lung carcinoma; PD-1, programmed death-1; PDL1, programmed death ligand-1; PDT, photodynamic therapy; PTT, photothermal therapy; ROS, reactive oxygen species; RT, radiotherapy; TAA, tumor-associated antigen; TIL, tumor-infiltrating lymphocytes.

1 | INTRODUCTION

The abscopal effect is a promising approach in cancer therapy that allows local therapies such as radiation therapy (RT), phototherapy, and others to treat focused and distant tumors. The term "abscopal effect" was first used by Mole to describe the immune response of a distant tumor to RT within the same organism [1]. The word abscopal effect means "away from the target site," derived from a Latin word in which the prefix ab- means "away from" and the suffix scopus- means "mark or target for shooting at." RT, in general, is a treatment method used to control localized tumors. However, RT has systemic antitumor effects apart from the targeted tumor by stimulating immune responses against the tumors.

Although the abscopal effect reduces the burden of chemotherapy and other combination cancer therapies, it is a rare occurrence [2]. Many factors contribute to the event, including the patient's immunity [3–6, 8], the type of RT used [7, 8], radiation time, and cancer itself [6, 9], as a result, the precise mechanism of this event is unknown and occurs only infrequently. Despite this, researchers worldwide are very keen on this event as it benefits producing systemic effects and long-term immunity against metastatic cancers. As previously stated, the occurrence occurred by chance. Researchers discovered ways to enhance the abscopal effect by combining it with other therapies and modalities. Immunotherapy and RT are two of the most well-known methods [10–13]. Many studies have shown that the abscopal effect is produced not only by RT alone but also by other local cancer therapies such as photodynamic therapy (PDT) [14, 15], photothermal therapy (PTT) [16], cryoablation [17], high-intensity focused ultrasound [18], and so forth. Among all treatments, the RT-induced abscopal effect has received the most attention, either alone or in combination with immunotherapy [19].

Many studies have investigated the abscopal effect induced by RT alone or in combination therapy. We present an overview of the various modalities that produce the abscopal effect, including RT, the most prominent mechanism of the abscopal effect reported so far, and the other techniques used to boost the abscopal effect, different modalities, preclinical and clinical evidence, case reports, challenges, and future perspectives.

2 | DIFFERENT CANCER THERAPIES ELICITING THE ABSCOPAL EFFECT AND UNDERLYING MECHANISMS

2.1 | RT

RT is one of the most common cancer treatments, in which high doses of ionizing radiation are used to eradicate cancer cells. Extreme amounts of radiation destroy tumor cells or slow their progression by damaging their DNA beyond repair, allowing the cells to undergo apoptosis or necrosis, which the body can remove naturally. In general, a single radiation treatment is insufficient to damage DNA and cause cancer cells to die; it takes several days to several weeks of treatment.

2.1.1 | Various types of RT

RT is classified into two types based on radiation source: external beam RT (EBRT) and internal RT (IRT). The type of RT depends on the tumor type, tumor size, tumor location in the body, the proximity of the tumor to normal tissues that are vulnerable to ionizing radiation, the patient's health, medical records, and other patient-related factors such as age, sex, and other medical conditions, and whether any combination therapy is required in addition to the RT.

EBRT involves using a radiation source that is located outside the body. This therapy is typically applied locally, that is, to a specific body part. For example, radiation is applied only to the chest to treat lung cancer and not the entire body. Three-dimensional conformal RT, intensity-mediated RT (IMRT), image-guided RT, Tomotherapy®, and stereotactic radiosurgery or stereotactic body RT (SBRT) are examples of EBRT.

IRT is a treatment in which radiation is delivered through solids or liquids placed within the body. IRT is divided into two types based on the type of source placed in the body: brachytherapy (solid source) and systemic therapy (liquid source). Brachytherapy is a localized therapy used to treat a specific body part. A solid radiation source is implanted either inside or near the tumor. In systemic therapy, a liquid source generates radiation that travels through the blood to tissues throughout the body, monitoring and slaying cancer cells.

2.1.2 | RT and its role in the abscopal effect

As previously stated, RT can cause cell death by various mechanisms, resulting in apoptosis or necrosis via differential antigenic presentation and clearance mechanisms. Besides the mechanisms mentioned above, it has been discovered that cell death following RT may also be immunogenic and characterized by specific antigens released from the damaged tumor cell by RT called tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) [20], which can have the capability of stimulating an immune response specific to a tumor, where antigen-presenting cells (APCs) present them to cytotoxic T cells (cytotoxic/$CD8^+$ T cells), which detect and destroy both the primary and distant tumors. Along with TAA and DAMPs, cytokines secreted by irradiated tumor cells [21] promote immune cell trafficking. The immune system's contribution to the favorable effects of radiotherapy was first reported in 1979 [22]. The first evidence of the abscopal effect as an immune-driven phenomenon was reported after two decades [8].

2.1.3 | RT and immunogenic cell death (ICD)

ICD of radiation-induced tumor cells is associated with the discharge of TAAs and danger signals (release of DAMPs) that are critical for engaging and triggering dendritic cells (DCs) in a concentration-reliant manner [23]. Immunogenicity of cell death by DAMPs (calreticulin [CRT], high-mobility group box 1 [HMGB1], adenosine triphosphate [ATP]) encompasses the following mechanisms [20]:

Cytosolic CRT translocation to the cell surface

CRT is a chaperone present in the endoplasmic reticulum; it is involved in calcium homeostasis and regulates the calcium-dependent pathways. However, the endoplasmic reticulum (ER) stress causes the endocytic CRT to translocate after RT to the surface, triggering DCs and leading to tumor cell phagocytosis [23–25].

HMGB1 released into the extracellular environment

HMGB1 is a nonhistone protein that binds to chromatin. The disruption of the nuclear membrane after RT leads to the release of HMGB1 into the extracellular region, where it acts as a proinflammatory mediator and activates DCs due to its high affinity toward the toll-like receptor 4 (TLR-4), which is abundant on DCs. HMGB1 also acts as an agonist to the myeloid receptor for advanced glycation end products (AGER/RAGE), leading to phagocytosis [26].

Release of ATP from cytosol

After RT, ATP is released from the cytosol and binds to purinoceptors on the DC membrane. It activates the inflammation leading to interleukin-1β (IL-1β) secretion [27].

Along with the above three DAMPs, cytosolic DNA produced by the cGAS-STING (cyclic GMP AMP synthase stimulator of interferon genes) pathway has been identified as a new DAMP that triggers the secretion of Type I interferon, which increases the number of antitumor T cells [28]. The mechanisms result in increased cross-presentation of tumor antigens, which increases the number of tumor-specific cytotoxic T lymphocytes (CTLs) and eradicates the tumor. Figure 1 depicts the mechanism of the RT-induced abscopal effect.

The majority of the studies suggested that the RT-induced abscopal effect is immune-mediated [8]. The immune-mediating abscopal mechanism consists of the release of TAAs and DMAPs, including CALR (CRT), ATP, HMGB1, and heat-shock proteins (HSPs), and tumor necrosis factor-α(TNF-α), interferons (IFNs), and interleukins [29]. It was discovered that after radiation, levels of IFN-γ, chemokine ligand 9 (CXCL9), CXCL10, and CXCL 16 are increased [30, 31], which leads to increased T-cell drift and vascular penetration, thereby increasing the T effector cell intervention to the tumor location [31]. In addition, other factors produced after RT play a substantial role in ICD, such as an extracellular increase of Type 1 IFN, representing the tumor relapse effect of RT [32]. IFN-β also plays a role in T-cell activation following RT. It was discovered that RT-induced IFN-β had a role in generating the abscopal effect in non-small cell lung carcinoma (NSCLC) patients [2, 33–37]. After detecting cytosolic DNA produced by nuclear rupture by RT, activation of the cGAS-STING pathway produces an immune response by triggering IFN-β secretion, which is responsible for the emergence of antitumor T cells [28, 38]. Other studies have discovered the role of p53 on the abscopal effect, stating that the downstream pathway of p53 is required for the abscopal effect, but this was not further elaborated [39, 40]. A case report on a 63-year-old patient with metastatic NSCLC who received whole-brain RT (45 Gy in 15 fractions) and palliative radiation (30 Gy in 10 fractions) resulted in an abscopal effect with no chemotherapeutic or immunotherapeutic intervention [41]. Another case report on a 52-year-old patient with palatine tonsil follicular lymphoma who received low-dose radiotherapy of 2 Gy × 2 demonstrated an abscopal effect by eradicating the circulatory lymphoma, implying that a low dose RT can produce an abscopal effect [42].

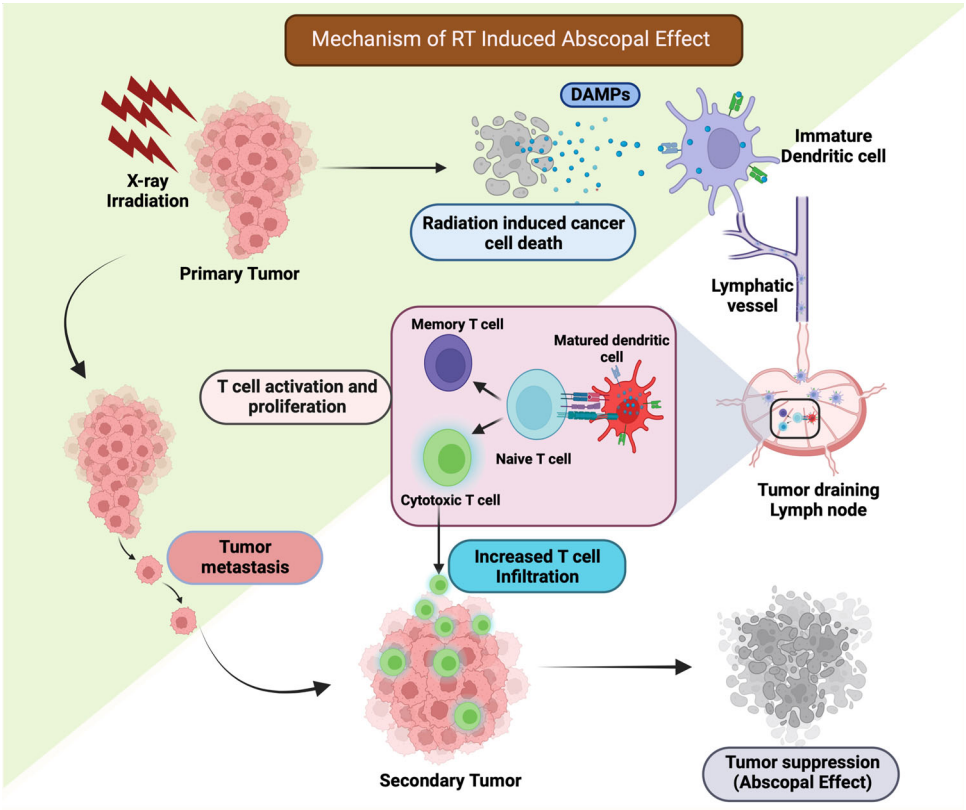

FIGURE 1 Mechanism of radiation therapy (RT)-induced abscopal effect. DAMPs, damage-associated molecular patterns.

2.2 | PDT

A photosensitizer and a specific wavelength of light are used in PDT [43]. When exposed to a particular wavelength of light, photosensitizers or photosensitizing agents produce reactive oxygen species (ROS), which are cytotoxic [44–46]. Each photosensitizer gets activated at a specific wavelength. The wavelength of the light decides how far it can travel in the body. The longer the wavelength, the deeper the penetration, so in general the photosensitizer with photoactivation at a longer wavelength will be more efficacious [44–46]. Tumor cell death by PDT includes direct damaging of cancer cells by ROS, damaging the tumor vasculature, resulting in the infraction of tumor cell and their death, and ICD by initiating an immune response, which is primarily a posttreatment response toward the tumor cells and is more long-lasting than others [43, 44, 47].

The clinical effects of PDT primarily involve two steps: first, the administration of photosensitizer, and second, the photoactivation of the administered photosensitizer at a specific wavelength, mostly 650–850 nm [48], The photoactivation occurs after a specific interval of time after administration of the photosensitizer, the time called drug to the light interval (DLI), based on which PDT is further classified into two types: (a) cellular PDT, where the DLI is high and allows for maximum photosensitizer redistribution in cellular compounds and (b) vascular PDT, where the DLI is significantly less, and the targeting is confined to tumor vasculature [43]. A photosensitizer's PDT efficiency is determined by its spectral properties and ability to produce a high quantum yield of triplet oxygen with a longer lifetime and high singlet oxygen quantum yield [49].

2.2.1 | PDT and the abscopal effect

As previously stated, tumor cell death by PDT is classified into three types: direct killing by ROS-induced autophagy or apoptosis or necrosis, tumor vasculature damage, and ICD. The first two are very quick and last for a brief period and are responsible for the third type, that is, ICD, which lasts for a more extended period and results in anticancerous innate and adaptive immune response [24, 50]. The main reason for developing PDT-induced antitumor response in targeted cancer cells is the release of kinases like protein kinase R-like ER kinase, inositol-requiring element-1, which are formed by unfolded protein response and integrated stress response [24], which leads to the release of stress-induced chaperons like CRT, HMGB1, and ATP [29, 50],

to maintain the homeostasis through an immunological response that produces innate and adaptive immunity against the tumors [29].

DAMPs are crucial for producing the abscopal effect. PDT can also produce the abscopal phenomenon by producing stress-induced DAMPs. The first case of PDT-induced abscopal effect was reported in 2007 in a 64-year-old patient suffering from multifocal angiosarcoma, who was treated with PDT using Fotolon as a photosensitizer and irradiated with a 665-nm laser beam, delivered at a rate of 80–150 mW/cm^2 after 3 h of administering Fotolon [14]. Following that, numerous studies on the long-term systemic effects of PDT and the abscopal effect after PDT were conducted; a study on Lewis lung carcinoma (LLC) cells after Photofirin^{TM} PDT demonstrated the expression of two prototypical DAMPs, CRT and HMGB1, both in vitro and in vivo [21]. The study found that after 1 h of PDT treatment, the number of CRT surface expressions increased both in vitro and in vivo. This study also found increased HMGB1 in macrophages after 16 h of incubation with PDT-treated LLC cells [21]. Phthalocyanine derivatives are a class of photosensitizers known for their impressive PDT outcomes. A study reported the fabrication of aluminum phthalocyanine (AlPc) nanoemulsion and its PDT efficacy using the 4T1 tumor-bearing mice model. The microtomography and histopathological analysis showed that AlPc nanoemulsion successfully eradicated both the primary tumor and metastatic lung tumor [51]. In a similar study, zinc hexadecafluorophthalocyanine ($ZnF_{16}Pc$) based PDT also caused the suppression of primary and metastatic tumors in the murine 4T1 model by inducing the abscopal effect [52]. To investigate the systemic effects of PDT in colorectal cancer, a study used IR700DX-6T photosensitizer against MC38 tumor-bearing mice. This photosensitizer was designed to target a mitochondrial 18 kDa translocator protein (TSPO) that is overexpressed in colorectal cancer. The TSPO-targeted PDT suppressed distant tumor growth by activating dendritic and CD^{8+} T cells. Immunofluorescence analysis showed high levels of two DAMP molecules, CRT and HSP70, which trigger ICD [53].

2.3 | Cryoablation

Cryoablation involves killing cells through the in situ cyclic application of low temperatures to the targeted tissue, resulting in an ice crystal, a phenomenon known as the Joule-Thomson effect. The freezing temperature determines the formation of ice crystals inside the cytoplasm of cells or the extracellular space of the targeted tissue. Ice crystals form in extracellular spaces at low freezing temperatures, causing surrounding cells to lose solvent and shrink to balance osmotic pressure. However, during the thawing stage, the cells absorb the solvent from the extracellular space, resulting in cell burst. Ice crystals formed inside the cells cause damage to the lipid membrane and release all intracellular components. This method is predominantly used to treat benign and malignant primary tumors [54]. During the early stages of cryoablation system development, the use of bulky refrigerants such as liquid nitrogen through noninsulated cannular devices caused many adverse effects in normal tissues; however, these problems were resolved by various technological advancements, such as the Food and Drug Administration's development of an argon-helium super-conducting targeted surgical system (Endocare) in 1998 [54–56].

2.3.1 | Abscopal effects of cryoablation

Cryoablation has a distinct advantage over other therapies. It causes severe necrosis by disrupting the cell membrane and preserving the TAAs needed to activate an immune response against abscopal tumors [57]. The abscopal effects of cryoablation have been observed since 1970 [58] and much preclinical evidence has demonstrated the systemic immune effects of cryotherapy [59–64]. It was also observed that the antitumor immune response produced after cryoablation is tumor-specific; a study in C57BL/6 mice with MCA-10 fibrosarcoma showed that the cytotoxicity of lymphocytes harvested at weekly intervals after treatment was investigated against tumor antigens. It was observed that the cryoablated mice had significantly higher tumor cytotoxicity than surgically treated or untreated mice. This study also demonstrated that the cytotoxicity was tumor-specific, as the lymphocytes had no effect on antigens obtained from other types of tumors [59]. In a study on Vx2 rabbits and sarcoma 180 ICR mice, cryoablation resulted in a tumor-specific immune response against nontreated and rechallenged tumors [62]. Another study comparing the immunologic effects of cryoablation and surgical excision in adenocarcinoma induced-C3H/HeN mice and sarcoma-induced CDF1 mice found that cryosurgery produced significantly higher tumor specific immunity to resist rechallenged tumors than surgical removal [65]. Cryoablation-induced antitumor immunity was studied in Wistar rats with MT449A myosarcoma and Sprague–Dawley rats with Walker 256 carcinosarcoma. Cryosurgery caused complete tumor regression in both models, and they resisted the development of a second challenging tumor transplant [66]. In a recent pilot study on BALB/c mice implanted with 4T1-12B breast cancer cells, it was discovered that cryoablation induced a robust abscopal response through

an increase in the number of tumor-infiltrating lymphocytes (TILs) when compared to resection. Likewise suggested TILs as biomarkers for the abscopal effect caused by cryoablation in a breast cancer model [67]. A report on computed tomography-guided percutaneous cryoablation showed excellent tumor ablation in a 67-year-old patient suffering from neuroendocrine malignancy with hepatic metastasis. In several studies, tumor tissue was surgically removed using a cryoablation system. Cancer cell antigens were exposed during the freeze-thaw cycles due to cell membrane damage, inducing an immune response even at the distant tumor, that is, the abscopal effect [68, 69]. Cryotherapy accomplishes this by activating DCs and by inducing cytokine secretion, which is critical in antigen presentation and the antitumor immune response, respectively [70]. Similarly, the abscopal effect on the abscopal tumor was observed when a liquid nitrogen-treated tumor-bearing bone graft was reimplanted into a bone metastasis-induced female C3H model; however, this effect was synergistically enhanced when cryotherapy was used in combination with an immune checkpoint inhibitor (ICI) anti-programmed death-1 (PD1) therapy due to the induction of the T-cell response against tumors, which was absent in mice having frozen-autograft alone [71]. After 1 month of cryoablation treatment, the primary carcinoid tumor shrank by 90%, with no growth in the metastatic tumor [72]. A similar report demonstrated cryoablation-mediated abscopal effect in a 68-year-old female patient. The patient was diagnosed with ductal carcinoma in the right breast that caused metastasis in the regional lymph node. The cryoablation of breast tumors alone resulted in the complete regression of both tumors after 5 months of treatment. This study demonstrated axillary metastasis treatment through a cryoablation-induced abscopal effect [73]. The effectiveness of cryoablation has also been reported in metastatic head and neck cancer. A 70-year-old patient suffering from nasopharyngeal carcinoma for 20 years was diagnosed with metastasis in the hard palate, left side of the oropharynx, and left parotid. The patient underwent two freeze/thaw cycles of cryoablation at 50% and 25% power. After 8 months of treatment, magnetic resonance imaging showed complete ablation of the treated lesion and shrinkage of the metastatic tumor due to the abscopal effect [74].

3 | CHALLENGES IN PRODUCING THE ABSCOPAL EFFECT AND OVERCOMING THEM

Despite extensive research and preclinical and clinical evidence on abscopal effects or systemic antitumor immunity after various local cancer therapy modalities, the exact mechanism of its occurrence and reproducibility remains unclear. Some challenges are common for various modalities, and some are specific to a particular therapy. The challenges of producing an abscopal effect vary with the type of therapy used, but the common challenge with all the therapies is immune suppression. Here we have briefly explained the challenges of inducing the abscopal effect using RT, PDT, and cryoablation.

3.1 | Challenges to the RT-induced abscopal effect

Although many studies propose the abscopal effect followed by RT, the manifestation of the abscopal effect can be influenced by various factors. These include the type of irradiation, radiation dose, duration of irradiation, and type of cancer immune activity of the patient [3].

The abscopal effect is uncommon and is attributed to the aforementioned factors above. The suppressive effect of the tumor microenvironment is the principal cause of the abscopal effect's rarity. The suppressive environment includes cytokines released by tumor cells, such as transforming growth factor-β (TGF-β), immune checkpoint receptors expressed on T-cell surfaces, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA4) [75, 76], and programmed cell death ligand-1 (PDL1), which inhibit the T-cell functioning. The other immunosuppressive mechanisms of the tumor microenvironment include macrophages (M2), regulatory T (Treg) cells, immature DCs, and myeloid-derived suppressor cells (MDSCs) [77]. The immune-suppressive mechanism is depicted in Figure 3.

The host immune system is one of the significant challenges of the RT-induced abscopal effect. Early studies on RT of melanoma [78] and papillary adenocarcinoma [79] demonstrated that radiotherapy alone could produce the abscopal effect, and later studies suggest that the host's immunity plays a substantial role in radiotherapy-induced tumor killing. A study on syngeneic mouse models of fibrosarcoma demonstrates that the dose required to reduce the tumor growth in immunodeficient animal models is higher compared to that of immunocompetent animal, this study also demonstrates that the metastasis in the immunodeficient animal is higher compared to the immune-competent model, which suggests the impact of the intact immune system on RT response and metastasis [22]. Another preclinical study on mice bearing a syngeneic mammary carcinoma (67NR), treated with Flt3-L daily for 10 days after local RT of a single dose of 2 or 6 Gy to only one of the two tumors demonstrated that the abscopal effect is immune-mediated and requires T cells to mediate abscopal tumor inhibition [6]. Moreover,

this study also suggests that the abscopal effect is tumor-specific. Based on the data presented above, it is clear that the immune profile of the patients influences the abscopal effect, which varies from patient to patient and is related to genetic variation, diseased state, and so on; variabilities are difficult to diminish.

The major constraint for the RT-induced abscopal effect is the immune-suppressive tumor microenvironment known as an immune escape, one of the hallmarks of cancers [80]. The immune-suppressive mechanism of tumor cells is depicted in Figures 2 and 3. Depleted levels of oxygen and the rapid growth of tumors cause chronic inflammation, mediated by overexpression of tumor necrosis factor, IL-1β, IL-6, IL-10, and TGF-β [77, 81–84], and the recruitment of local immune-suppressive cells like tumor-associated macrophages (M2 macrophages) [85], MDSCs, and Treg cells [77] cumulatively produce adaptive immunity suppression.

Other regulatory mechanisms that will retard the T-cell activation include PD1 and PDL1, leading to T-cell exhaustion; CTLA4 and OX 40 act as immune checkpoints [77]. Many studies found a way to avoid immune suppression by using immunotherapy combined with RT [86, 87], immune checkpoint blockade, that is, anti-CTLA4 [19, 88, 89], dual checkpoint blockade therapy using ipilimumab (anti CTLA4 antibodies), nivolumab (anti-PD1 antibodies) after dose painting-SBRT, shows potential abscopal effect in renal cell carcinoma) [90].

The dose and dose fractions of the radiation also influence the initiation of the abscopal effect. It was

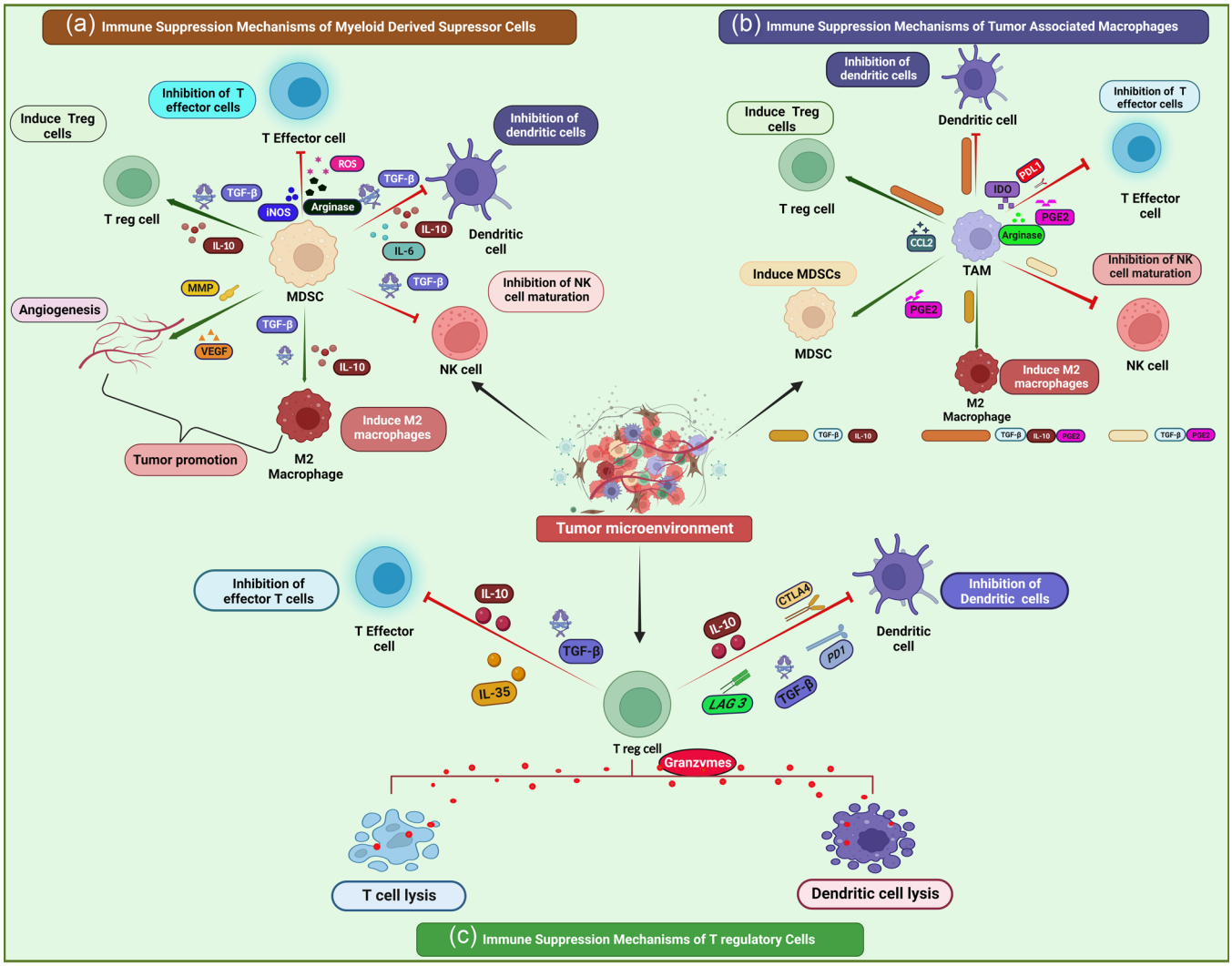

FIGURE 2 Immune suppressive cells of the tumor microenvironment. CL2, chemokine (C-C motif) ligand 2; CPDL1, programmed death ligand-1; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; IDO, indoleamine 2,3-dioxygenase; IL-6, interleukin 6; IL-10, interleukin-10; iNOS, inducible nitric oxide synthase; LAG-3, lymphocyte activating gene 3; MMP, matrix metalloproteases; NK cell, natural killer cell; PD1, programmed death-1; PGE2, prostaglandin E2; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

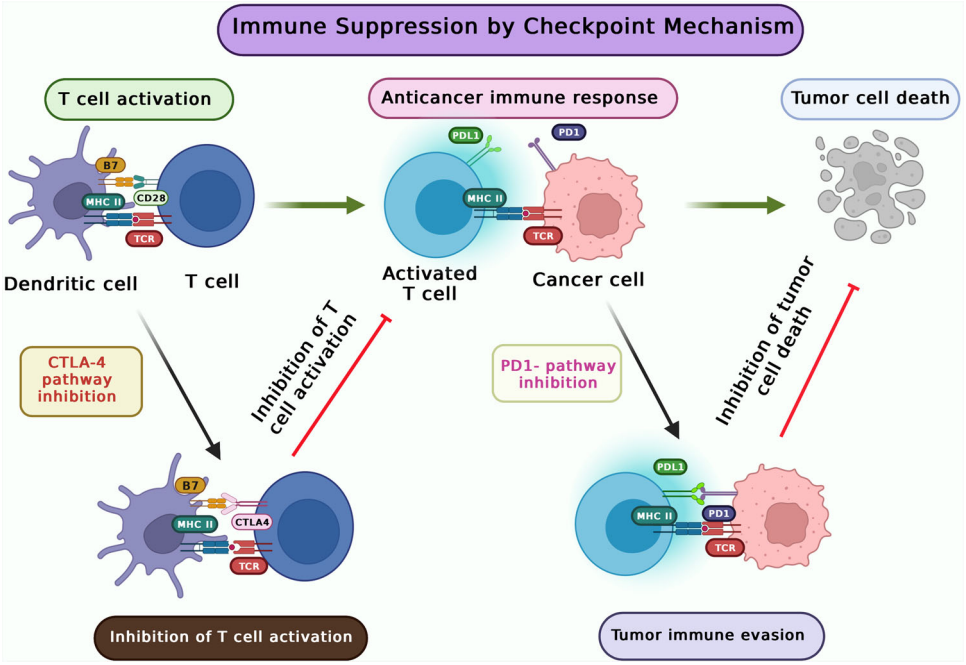

FIGURE 3 Immune suppression by checkpoint mechanism. CTLA4, cytotoxic T-lymphocyte-associated antigen 4; MHC-II, major histocompatibility complex II; PD1, programmed death-1; PDL-1, programmed cell death ligand-1; TCR, T-cell receptor.

observed that the abscopal effect after RT alone and combined RT + immunotherapy was affected by the dose of radiation. A study found that the fractional radiation dosing (8 Gy × 3) increased IFN-β secretion compared to single doses of 20 and 30 Gy by impeding the expression of three prime repair exonuclease 1 (TREX 1). It is reported that the enzyme TREX 1 attenuates the immunogenicity by degrading the cytosolic DNA accumulated after nuclear degradation upon radiation, which in turn triggers the secretion of IFN-β by the cGAS-STING pathway [28, 38]. A study demonstrated that fractionated doses of radiation could induce the abscopal effect when combined with anti-CTLA4 antibody immune therapy, whereas a single dose of radiation could not [91]. In another Phase I trial on patients with metastatic NSCLC and melanoma, it was found that both the hypofractionated (24 Gy × 3) and single dose (17 Gy) could induce the systemic immune response when combined with immunotherapy using pembrolizumab (PD1 antibodies) [92]. Furthermore, the systemic effects of HFRT were discovered to differ depending on fraction dose size and splitting schedule [93]. In a study on 4T1 tumor-bearing mice, fractionated doses of 8 Gy × 3, 13 Gy × 1 have shown improved antimetastatic potential, higher production of HMGB1, and lower expression of proinflammatory cytokines such as IFN-λ, TNF-α, IL-6, and IL-1 [93]. In another study on the B16-CD133 tumor-bearing mice model and 4T1-bearing mice model, it was observed that extended scheduled HFRT showed similar systemic effects to that of short scheduled HFRT; this study also reports the role of T-cell infiltration in the systemic effects of RT [94]. Many of the studies where dose and dose fractions affect the RT-induced abscopal effect are furnished in Table 2.

The other challenge is the type of radiation used. It is still unclear which RT produces the best abscopal effect, as each has advantages and disadvantages. It is difficult to find the ideal RT to produce the required abscopal effect, resulting in tumor regression. A recent study demonstrated that adrenergic stress would retard the antitumor immunity of local radiation [95].

3.1.1 | Overcoming the challenges of RT-induced abscopal effect

To avoid the problems mentioned above, many researchers conducted numerous clinical and preclinical studies to investigate how to increase the incidence of the abscopal effect in metastatic tumors. The following are methods for improving the abscopal outcome after RT, combination therapy with ICIs, immunoadjuvant therapy, antigen-capturing nanoparticles, smart RT biomaterials, and appropriate radiotherapy modes.

Using ICIs in combination with RT has a high success rate in producing a significant abscopal effect, and many clinical trials are currently underway [96]. Table 2 shows the data regarding the combination of RT with immuno-therapy, immunoadjuvant therapy with RT, and different

types of RTs used to treat different cancers. A recent study proposed that additional low-dose RT of distant tumors, combined with HFRT and immune checkpoint inhibitors, could improve systemic immune response in a bilateral tumor model and patients with Stage IV NSCLC [97]. A triple combination therapy consisting of radiation alone (XRT), anti-PDL1, and SHP-2 inhibitor (SHP099) demonstrated significant antitumor effects in anti-PD1-resistant NSCLC mouse models by increasing the cytotoxic T-cell to Treg cell ratio [98]. The addition of antigen-capture NPs may increase the incidence of RT-induced abscopal effect. Intratumoral injection of mesoporous silica NPs (MSNs) into primary tumor after irradiation (8 Gy for 3 days) resulted in both primary and secondary tumor regression in hepatocellular carcinoma models, implying that MSN can be used as an immunoadjuvant in situ cancer vaccines in conjunction with radiotherapy [99]. Using novel neoadjuvant stimulated RT-induced abscopal effect is another strategy for overcoming immune suppression by the tumor microenvironment. In a recent study, RT in combination with valproic acid showed a significant abscopal effect compared to RT alone in breast cancer models owing to its M1 polarization activity, thus increasing the number of inflammatory cytokines at the tumor sites [100]. In another study, the combination of RT and 2-hexyl-4-pentylenic acid (HPTA), a valproic acid derivative, demonstrated a significant abscopal effect by M1 polarization of tumor-associated macrophages in a breast cancer model, implying that HPTA could be used as a novel neoadjuvant to stimulate RT-induced abscopal effect in the treatment of breast cancer [101]. A study reported that the combination of metformin and RT suppressed the growth of nonirradiated lung metastasis in a murine rectal cancer model [102]. The combination of PI3K/inhibitor (BR101801) and XRT in the CT-26 syngenic mouse model demonstrated an abscopal effect by increasing the cytotoxic T-cell to T-reg cell ratio, insinuating that the combined therapy of PI3K/inhibitor and RT converts immunologically cold tumors into immunologically hot tumors [103].

Although immunotherapy boosts the abscopal effect, some studies report that it may lead to immune-related adverse events [104, 105]; it was also reported that the adverse events of anti-CTLA4 are severe compared to anti-PD1 drugs [85, 86]. Other factors that influence the increase of the abscopal effect, such as the type of RT and timing of therapy, that is, immunotherapy after RT or before RT, will also affect the boosting of the abscopal effect. Many studies have also found that immunoadjuvant therapy can efficiently increase the abscopal effect of RT [36, 106]. Various studies discovered the impact of different factors such as the sequence of treatments, type of tumor, irradiation dose, irradiation time, and the type of RT, which influence the increase of abscopal effect furnished in Table 1.

3.2 | Challenges to the PDT-induced abscopal effect

PDT has evolved into effective local cancer therapy. PDT has an advantage over RT because it is safer and less harmful. Previously, it was only used to treat local solid tumors and was ineffective against metastatic lesions [118], but subsequent research demonstrated that PDT has systemic effects [119]. Many studies have shown that PDT can elicit abscopal effects and a systemic antitumor immune response [14, 120]. The antitumor efficacy of PDT depends upon the photosensitizer used and its ability to produce ROS for an extended period of time [49], which is a limitation of PDT.

PDT's significant barriers to producing a prominent abscopal and long-term systemic immunity against cancer are:

- The ROS produced after PDT has a shorter lifespan and may not be effective against the tumor, that is, ineffective cell stress leads to the offensive production of DAMPs and neoantigens, which plays a vital role in ICD.
- The tumor microenvironment includes hypoxia conditions that reduce the amount of ROS at the tumor site and immunosuppressive mechanisms. One of them is indoleamine 2,3-dioxygenase (IDO) overexpression, an enzyme that inhibits T-cell function, and immune checkpoint mechanisms like CTLA4 and PD1.

3.2.1 | Overcoming the challenges of PDT-induced abscopal effect

An important aspect to consider when producing a prominent abscopal effect using PDT includes the type of photosensitizer used. A photosensitizer should produce enough ROS over time to cause tumor ablation while also producing an adequate amount of TAAs and DAMPs [27, 121–126]. Second, we can use a drug delivery system [127–133] to convert the tumor hypoxia into a normoxic state and increase the amount of ROS generation. Third, it is always important to understand the type of immune suppression, like whether it is caused by the tumor microenvironment, such as overexpression of arginase, IDO, which inhibits the expression of T effector cells, or it is caused by immune checkpoint blockade, so we can use an appropriate combination therapy or develop a

TABLE 1 Various clinical and preclinical studies of combination therapies with RT show increased abscopal effect.

Sl. no	Type of RT used	Dose of radiation	Period of therapy	Type of combination therapy used	Type of tumor	Sequence of therapies	Ref.
1	EBRT	35 Gy in 10 fractions	14 days	GM-CSF	Metastatic solid tumors	Concurrent GM-CSF injections started from the second week of RT	[36]
2	SBRT	For lung/bone lesion: 16 and 24 Gy in 2 levels	3–5 days	Anti-CTLA4 antibody (ipilimumab)	Melanoma	Anti-CTLA4 antibody injected after RT	[107]
3	SBRT	Liver/subcutaneous lesion: 12 and 18 Gy in 2 levels	3–5 days	Anti-CTLA4 antibody (ipilimumab)	Melanoma	Anti-CTLA4 antibody injected after RT	[107]
4	SARRP	20 Gy	1 day	Both anti-CTLA4 and anti-PDL1	B16-F10 Melanoma	Both sequential and concurrent	[107]
5	SARRP	8 × 3 Gy	3 days	Both anti-CTLA4 and anti-PD1	TSA breast cancer	Immunotherapy is given before RT	[107]
6	EBRT	3000 cGy in 10 fractions	12 days	Pembrolizumab (anti-PD1 antibody)	Hodgkin's lymphoma	RT was given between two pembrolizumab infusions	[108]
7	SARRP	6 Gy	3 days	Immunoadjuvant therapy by anti-CD-40 nanoparticles	Lung cancer	Concurrent	[106]
8	EBRT	8 Gy × 3	3 days	DC-stimulating growth factor Flt3-L	67NR mammary carcinoma	Concurrent	[109]
9	SARRP	20 Gy × 1	1 day	Anti-CTLA4 or anti-OX40	CT-26 Colorectal cancer	Concurrent	[110]
10	SBRT	500 cGy × 4	14 days	Anti-PD1 (nivolumab) and Sandostatin	Neuroendocrine cervical carcinoma	SBRT 2 weeks after immunotherapy was initiated	[111]
11	DP-SBRT	18 Gy to the tumor surface and 27 Gy to the center of the lesion over 3 fractions	180 days	Anti-CTLA4 (ipilimumab) and anti-PD1 nivolumab concurrently	Renal cell carcinoma	Immunotherapy after DP-SBRT	[90]
12	IMRT	48 Gy in 24 fractions	14 days	Adoptive T-cell immunotherapy	Recurrent gastric cancer	Concurrent	[112]

TABLE 1 (Continued)

Sl. no	Type of RT used	Dose of radiation	Period of therapy	Type of combination therapy used	Type of tumor	Sequence of therapies	Ref.
13	Brachytherapy	8 Gy × 3	3 days	Immunostimulatory anti-PD1, anti-CD-137, or anti-rat IgG control antibodies	MC38 Colorectal cancer	Concurrent	[23]
14	CIRT	73–6 Gy in 16 fractions	28 days	–	Recurring colorectal cancer	None	[113]
15	WBRT SRT Palliative RT	12–39 Gy 15–30 Gy 30 Gy in 10 fractions	180 days	Anti-PD1 therapy	Metastatic melanoma, NSCLC, RCC	Either before or after the RT or on both before and after RT	[35]
16	EBRT	Single-dose of 10 Gy	1 day	Anti-PD1 therapy	B16F10GP melanoma	Immunotherapy after RT	[114]
17	HFRT	Cohort I 1.8 × 3 Gy Cohort II 17 Gy × 1 (6 patients in each cohort)	21 days	Anti-PD1 (pembrolizumab)	NSCLC/melanoma	Pembrolizumab starts 1 week before first fraction of HFRT and continues for 3 weeks	[92]
18	EBRT	40 Gy IN 20 fractions	–	Anti-PD1	Hodgkin's lymphoma	Nivolumab of two doses concurrently	[89]
19	HDR-ISBT	35 Gy in 5 fractions	3 days (2 times a day with 6 h intervals	Anti-PD1	Metastatic renal carcinoma	Nivolumab 10 days before the HDR-ISBT and after 9 days of completing HDR-ISBT	[115]
20	SBRT	4000 cGy in 5 fractions	3 days	Somatostatin agonist	Typical metastatic pulmonary carcinoid	Lanreotide with concurrent therapy	[116]
21	SBRT	50 Gy in 4 fractions or hypofractionated doses 45 Gy in 15 fractions	–	Anti-PD1 (pembrolizumab)	Stage IV NSCLC	Concurrent	[117]

Abbreviations: CIRT, carbon ion radiation therapy; DP-SBRT, dose painting-stereotactic body radiation therapy; GM-CSF, granulocyte-macrophage-colony-stimulating factor; HDR-ISBT, high dose rate-interstitial brachytherapy; HFRT, hypofractionated radiation therapy; IMRT, intensity-modulated radiation therapy; NSCLC, non-small cell lung carcinoma; PD1, programmed death-1; PDL1, programmed cell death ligand-1; RCC, renal cell carcinoma; RT, radiotherapy; SARRP, small animal radiation research platform; SBRT, stereotactic body radiation therapy; SRT, stereotactic radiation therapy; TSA, trichostatin A; WBRT, whole-brain radiation therapy.

novel drug delivery system, which can overcome the above-stated challenges. Many studies have overcome these obstacles by the combination of PDT with drugs such as IDO inhibitors [134–136], immune adjuvants, immune checkpoint blockade drugs [10, 137, 138], and HIF1 inhibitors like acriflavine [139]. A recent study reported the combination of 5,10,15,20-tetra(*p*-benzoato) porphyrin (TBP) photosensitizer with a TLR agonist CpG oligodeoxynucleotide to promote DC maturation. High DC maturation allows effective antigen presentation and thereby enhances PDT-induced ICD. The synergistic effects of TBP and CpG generated a strong abscopal effect and caused >97% regression of both primary and secondary tumors [140]. CD73 blockade is another strategy to enhance PDT-mediated ICD. The CD73 enzyme hydrolyzes the ATP molecules produced after PDT to activate immune responses. ATP hydrolysis generates ADO, which acts as an immunosuppressor and blocks cytotoxic T-cell-mediated immune response. A study reported the combination of anti-CD73 antibody with rose bengal photosensitizer and doxorubicin against TNBC. The synergistic effects of chemo-PDT with CD73 blockade effectively suppressed lung metastasis [141]. One more example of PDT-based triple-combination therapy for systemic anticancer effects has been reported against uveal melanoma, using a combination of chlorin e6 photosensitizer with ripasudil and anti-PD-L1 antibody. Ripasudil is a rho-kinase inhibitor that shows immune-stimulatory effects by increasing APCs′ phagocytic and tumor antigen processing activity [142]. Metformin is a hypoglycemic drug that has been extensively explored in cancer therapeutics recently. It can downregulate PD-L1 expression on cancer cells, and when combined with PDT, it can overcome tumor hypoxia by reducing the oxygen consumption rate in the mitochondrial respiratory chain. A combination of IR775 photosensitizer and metformin has shown promising suppression of metastatic tumors due to enhanced photodynamic immune effects [143]. A recent study also suggested that combining PDT and PTT produces an abscopal effect in TNBC [144]. Many studies demonstrated that combining PDT with immunotherapy and hypoxia-elevated nanomaterials could improve systemic antitumor immunity [145]. Table 2 displays the results of various combinations used with PDT to elicit the abscopal effect.

3.3 | Challenges in cryoablation-mediated abscopal effect

The effectiveness of cryoablation-induced abscopal effect on cancer cells is mainly dependent on the Joule-Thomson effect, which is killing the cells by appropriate freeze-thaw cycle [159]. Even though cryoablation therapy was found to be effective in treating local and abscopal tumor tissues, it has certain limitations to be addressed.

The potential challenge is the development of immune suppression rather than immune stimulation leading to increased tumor metastasis [160–165]. It was observed that cell death by cryoablation is done by two major mechanisms, that is, by necrosis at cells near the probe and apoptosis at cells far from the probe, and it was also observed that these two mechanisms elicit different types of immune responses [166, 167]. It is unclear which of these two mechanisms can produce antitumor immune response or immune-suppressive mechanisms. Some studies suggest that necrosis leads to the antitumor immune response and apoptosis causing immunosuppression or increasing the tumor metastasis [166, 168, 169] and some studies suggest the opposite [170–172]. So, it is a challenge to balance these necrotic and apoptotic responses of cryoablation to get an antitumor immune response to prevent metastasis and show an abscopal effect. Even if either of the mechanisms of primary cell death produces the antitumor immune response, which can kill the secondary tumors, the chances of producing the abscopal effect are less due to the immune checkpoint mechanism and immunosuppressive tumor microenvironment.

3.3.1 | Overcoming the challenges of a cryoablation-induced abscopal effect

As discussed earlier, the major challenges in producing the abscopal effect using cryoablation are balancing the primary tumor death mechanisms, that is, apoptosis and necrosis to produce antitumor immune responses and reduce the immunosuppression. It is difficult to control the method to maintain a balance between apoptosis and necrosis by cryoablation, although it can be solved by reducing the immunosuppression, that is, by using immunotherapy against the immunosuppressive TME and immune checkpoint mechanism. Many studies have shown successful abscopal effects using cryoablation in combination with immunotherapy [173]. A study on mice with prostate cancer found that cryoablation can induce an antitumor immune response by decreasing the number of T-reg cells, but it is time-dependent and requires an appropriate treatment interval of cryoablation. This study also found that combining anti-CTLA-4 therapy with cryoablation enhanced the effect of cryoablation on secondary tumor metastasis when compared to anti-CTLA-4 therapy alone or cryoablation

TABLE 2 Various clinical and preclinical data show the abscopal effect with PDT alone or in combination with other therapies.

Sl. no.	Tumor type	Photosensitizer used	Combination therapy used	Type of carrier system used	Ref.
1	TNBC	Chlorophyll extracted from spinach	Photothermal therapy	Self-assembled fluorosome polydopamine complex	[144]
2	Breast cancer	Protoporphyrin IX (PpIX)	IDO inhibitor, navoximod NLG919	Liposomes (PpIX-NLG-loaded liposomes)	[146]
3	Colon carcinoma	Bremachlorin	Antagonistic CTLA-4-blocking antibody	–	[137]
4	Breast cancer	Chlorin e6 (Ce6)	Anti-PDL-1	pH-responsive nanoparticles	[147]
5	RCC	Padeliporfin	Anti-PD-1 and anti-PDL-1	–	[148]
6	Breast cancer	Pyrolipid	Anti-PD-L1	Zinc pyrophosphate nanoparticles loaded with pyrolipid	[149]
7	Osteo sarcoma	Phthalocyanine	Anti-PD-L1	ZnPc/BSA nanoparticle	[150]
8	mTNBC	Inorganic photosensitizer AuNCs	TME-responsive oxygen producer nanoparticles	Core-shell gold nanocage coated with manganese dioxide	[127]
9	Breast cancer	Chlorin e6 (Ce6)	Anti-CTLA4 and imiquimod (R837)	Light-triggered gelation system containing Ce6 and RPNPs (imiquimod-loaded nanoparticles)	[151]
10	Breast cancer	Chlorin e6 (Ce6)	Anti-PD-L1	Self-assembled nanoparticles of Ce6 and anti-PD-L1	[152]
11	Colorectal cancer	Chlorin e6 (Ce6)	Toll-like-receptor-7 agonist imiquimod (R837) + anti-CTLA 4	Upconversion nanoparticles (UCNP-Ce6-R837)	[153]
12	Breast cancer	Protoporphyrin IX (PpIX)	–	Photochemical internalization using pH low insertion peptide (pHLIP)	[125]
13	TNBC	Protoporphyrin IX (PpIX)	IDO inhibitor 1-methyl tryptophan (1MT)	Chimeric peptide nanoparticles containing caspase-responsive sequence Asp–Glu-Val–Asp	[15]
14	Melanoma	Chlorin e6 (Ce6)	Synergistic therapy by glucose oxygenase	CRET-based biomimetic nanoreactor hollow mesoporous silica nanoparticles	[154]
15	4T1 tumors	Boron difluoride dipyrromethene (BODIPY)	Vadimezan (a tumor-vascular disrupting agent)	Dual-functional organic nanoconjugate containing both BODIPY and VDA	[126]
16	CT-26 tumors	Porphyrinic metal-organic frameworks	Tirapazamine an hypoxia-induced prodrug + anti-PD-L1	Lanthanide-doped upconversion nanoparticles	[155]
17	4T1 tumors	ER-targeting photosensitizer TCPP-TER	–	Reduction-sensitive polymeric PEG-(Ds-sP) nanoparticles	[156]

(Continues)

TABLE 2 (Continued)

Sl. no.	Tumor type	Photosensitizer used	Combination therapy used	Type of carrier system used	Ref.
18	4T1 tumor model	Chlorin e6	Bee venom melittin	SA-coated boehmite organic-inorganic scaffold loaded with Ce6, and bee venom melittin, anchored by a boehmite nanorod structure	[157]
19	4T1 tumor model	TCPP	NK cell membrane immunotherapy	NK cell membrane-coated TCPP-loaded polymeric nanoparticles	[158]
20	B16-F10 melanoma	Pheophorbide A	FlaB-Vax, a TLR5 solid agonist	Liposome-based nanosystem (Lipo-PhA)	[138]
21	Colon carcinoma	TBP	Anti-PD-L1	Nanoscale metal–organic framework Fe-TBP	[132]

Abbreviations: CTLA4, cytotoxic T-lymphocyte-associated protein 4; Ds-sP, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[amino-(polyethylene glycol)-2000]; FlaB-Vax, flagellin-adjuvanted tumor-specific peptide vaccination; PD1, programmed death-1; PDL-1, programmed cell death ligand-1; TBP, 5,10,15,20-tetra(*p*-benzoato) porphyrin; TCPP-TER, 4,4′,4″,4‴-(porphyrin-5,10,15,20-tetrayl) tetrakis(*N*-(2-((4-methylphenyl) sulfonamido)-ethyl) benzamide; TCR, T-cell receptor; TNBC, triple-negative breast cancer.

alone [174]. In one study, the cryoimmunotherapy was used to treat metastatic lesions; in this, eight 17-gauge cryoablation probes were inserted into the right renal mass under CT fluoroscopy guidance, then two 10 min freeze cycles with 8-min thawing in between were used. Posttherapy monitoring through positron emission tomography scan revealed that cryoablation lysed the tumor cells, and TAAs were released and presented onto the T cells, further differentiated into cytotoxic T cells by local administration of nivolumab, which further reduced the growth of micrometastatic tumors, providing the systemic effect [17]. Cryoablation has also been employed in combination therapy in clinical trials. A study reported a combination of cryoablation and immunotherapy for the treatment of metastatic cervical carcinosarcoma in a 58-year-old patient. After cryoablation, the patient was treated with pembrolizumab, which resulted in a complete response after 3 months [175]. Similarly, the combination of cryotherapy with ipilimumab and nivolumab has also been investigated on 16 patients suffering from metastatic soft tissue sarcoma. Seven out of 16 patients got the clinical benefits of this combination therapy [176]. Table 3 shows the various clinical trials that are currently underway to treat various metastatic cancers using a combination of cryoablation and immunotherapy.

4 | CONCLUSIONS AND FUTURE PERSPECTIVES

Even six decades after the first-ever reporting of the abscopal effect, it remains the prime choice of interest for many cancer researchers worldwide due to the benefit of producing a robust and long-term systemic antitumor immunity against deadly cancers by inhibiting tumor metastasis and causing tumor regression with localized therapy. It will also lessen the need for toxic chemotherapeutic drugs. Despite decades of extensive research, no research has provided a robust mechanism of the abscopal effect that is reproducible. Many clinical and preclinical studies proposed various methods to induce abscopal effects of different therapies, which are, unfortunately, nonreproducible and specific to cancer type or patient and have their disadvantages; for example, the combination of immunotherapy could produce induced abscopal effects. Still, it leads to immune-related adverse events, and to counter these adverse events, immunosuppressive drugs are used, which retard the systemic antitumor immunity. The challenge is to devise a strategy that considers all the possible variables, such as tumor type, patient immunity, and other physiological factors, and

TABLE 3 List of a few clinical trials on the combination of immunotherapy and cryoablation is currently underway.

Sl. no.	Combination therapy used	Type of tumor	Clinical trial phase and recruitment status	Sponsor	NCT number
1	Ipilimumab Nivolumab	Early-stage breast cancer	NA/active not recruiting	Memorial Sloan Kettering Cancer Center	NCT0283233
2	Ipilimumab Nivolumab	Triple-negative breast cancer	Phase II/recruiting	Heather McArthur	NCT03546686
3	Therapeutic DCs, cyclophosphamide, ipilimumab	Prostate cancer	Phase I/completed	Alden Cancer Therapy II	NCT02423928
4	Degarelix, pembolizumab	Oligometastatic prostate cancer	NA/completed	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	NCT02489357
5	Tremelimumab	Metastatic kidney cancer	Early Phase I/completed	M. D. Anderson Cancer Center	NCT02626130
6	Peptide receptor radionuclide therapy (PRRT), pembrolizumab	Neuroendocrine tumors and liver metastases	Phase II/recruiting	Nicholas Fidelman, MD	NCT03457948
7	Pembrolizumab	Advanced and metastatic renal cell carcinomas	Phase I/withdrawn (the study was closed due to extremely low accrual, as well as a change in care when using the study drug	University of California, Irvine	NCT03189186
8	Durvalumab, tremelimumab	Hepatocellular carcinoma (HCC) or biliary tract carcinomas (BTCs)	Phase II/active not recruiting	National Cancer Institute (NCI)	NCT02821754
9	Pembrolizumab, therapeutic autologous DCs	Stage III and IV melanoma that cannot be removed by surgery	Phase I/II active not recruiting	Mayo Clinic	NCT03325101
10	DC therapy, pembrolizumab, pneumococcal 13–valent conjugate vaccine	Non-Hodgkin's lymphoma	Phase I/II/active	Mayo Clinic	NCT03035331
11	NK immunotherapy	Recurrent sarcoma	Phase I/II/completed	Fuda Cancer Hospital, Guangzhou	NCT02849366
12	NK immunotherapy	Recurrent pharyngeal cancer	Phase I/II/completed	Fuda Cancer Hospital, Guangzhou	NCT02849327
13	Activated CIK and CD3-MUC1 bispecific antibody	Advanced liver cancer	Phase II/withdrawn (no participants enrolled)	Fuda Cancer Hospital, Guangzhou	NCT03484962
14	NK immunotherapy	Advanced breast cancer	Phase I/II/completed	Fuda Cancer Hospital, Guangzhou	NCT02844335
15	NK immunotherapy	Recurrent cervical cancer	Phase I/II/completed	Fuda Cancer Hospital, Guangzhou	NCT02849340

Abbreviations: CIK, cytokine-induced killer; DC, dendritic cell; MUC 1, mucin 1; NA, not applicable; NK, natural killer cell.

produces a robust abscopal effect. To produce a robust and reproducible abscopal effect, it is necessary to investigate all possible biomarkers related to the abscopal responses of various local therapies, and to find the exact immunosuppressive mechanism elicited against antitumor immune response, so that one can use a precise immunotherapy to combat the immunosuppression. It may be possible to use a nanotheranostic approach in which NPs are loaded with predictive biomarkers and a prognostic indicator and to design a strategy that could be multifarious and addresses all potential barriers that retards the abscopal effect.

AUTHOR CONTRIBUTIONS

Sadik Ali Mohammad: Conceptualization (equal); data curation (equal); methodology (equal); project administration (equal); visualization (equal); writing—original draft (lead). **Arshadul Hak**: Writing—original draft (supporting). **Sunil V. Pogu**: Writing—review and editing (supporting). **Aravind K. Rengan**: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); supervision (lead); validation (lead); writing—review and editing (lead).

ACKNOWLEDGMENTS

The authors would like to acknowledge the following agency: Figures 1–3 were created using BioRender.com.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data was generated. The article is entirely theoretical research.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

ORCID

Aravind K. Rengan http://orcid.org/0000-0003-3994-6760

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How to cite this article: Ali Mohammad S, Hak A, Pogu SV, Rengan AK. Radiotherapy, photodynamic therapy, and cryoablation-induced abscopal effect: challenges and future prospects. Cancer Innovation. 2023;2:323–345. https://doi.org/10.1002/cai2.53