Received: 12 December 2023 | Revised: 6 May 2024 | Accepted: 22 May 2024

DOI: 10.1002/cac2.12576

CANCER COMMUNICATIONS Open Access

REVIEW

Beyond success: unveiling the hidden potential of radiotherapy and immunotherapy in solid tumors

Yuze Wu[1] | **Ming Yi**[2] | **Mengke Niu**[1] | **Binghan Zhou**[1] | **Qi Mei**[1] | **Kongming Wu**[3,4]

[1]Department of Oncology, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P. R. China

[2]Department of Breast Surgery, Zhejiang University School of Medicine First Affiliated Hospital, Hangzhou, Zhejiang, P. R. China

[3]Cancer Center, Shanxi Bethune Hospital, Shanxi Academy of Medical Science, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, Shanxi, P. R. China

[4]Cancer Center, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P. R. China

Correspondence
Kongming Wu, Cancer Center, Shanxi Bethune Hospital, Shanxi Academy of Medical Science, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan 030032, Shanxi, P. R. China.
Email: wukm_lab@163.com

Qi Mei, Cancer Center, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, Hubei, P. R. China.
Email: borismq@163.com

Abstract

Immunotherapy, particularly with immune checkpoint inhibitors, has significantly transformed cancer treatment. Despite its success, many patients struggle to respond adequately or sustain long-lasting clinical improvement. A growing consensus has emerged that radiotherapy (RT) enhances the response rate and overall efficacy of immunotherapy. Although combining RT and immunotherapy has been extensively investigated in preclinical models and has shown promising results, establishing itself as a dynamic and thriving area of research, clinical evidence for this combination strategy over the past five years has shown both positive and disappointing results, suggesting the need for a more nuanced understanding. This review provides a balanced and updated

List of abbreviations: ICI, immune checkpoint inhibitor; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy; ISABR, immunotherapy and stereotactic ablative radiotherapy; IGRT, image-guided radiotherapy; CTLA-4, cytotoxic T lymphocyte-associated protein 4; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; RIT, radioimmunotherapy; OS, overall survival; TME, tumor microenvironment; APC, antigen-presenting cell; TAA, tumor-associated antigen; DAMP, damage-associated molecular pattern; HMGB-1, high-mobility group box 1; ATP, adenosine triphosphate; DLN, draining lymph node; MHC, major histocompatibility complex; dsDNA, double-stranded DNA; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; TBK1, TANK-binding kinase 1; IRF3, interferon regulatory factor 3; IFN, interferon; TNF, tumor necrosis factor; TREX1, three prime repair exonuclease 1; MDSC, myeloid-derived suppressor cell; TAM, tumor associated macrophage; LPS, lipopolysaccharide; iNOS, inducible nitric oxide synthase; CSF1, macrophage colony-stimulating factor; SABR, stereotactic ablative radiotherapy; CR, complete response; BED, biologically effective dose; MPR, Major pathological response; HFRT, hypofractionated radiotherapy; ORR, overall response rate; PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; DC, dendritic cell; MHC, major histocompatibility complex; NK, natural killer; Treg, regulatory T cell; LA, locally advanced; CRT, chemo- radiotherapy; cCRT, concurrent chemo- radiotherapy; sCRT, sequential chemo- radiotherapy; CFRT, conventionally fractionated radiotherapy; STING, stimulator of interferon genes; CXCL, C-X-C motif chemokine ligand; TIL, tumor infiltrating lymphocytes; Foxp3, forkhead box protein P3; TGF-β, transforming growth factor-β; CCL, C-C motif chemokine; CCR, C-C chemokine receptor type; YTHDF2, YT521B homology domain family 2; AE, adverse effects; TPS, tumor proportion score; SCLC, small cell lung cancer; LDHRT, low-dose hypofractionated radiotherapy; MSS, microsatellite stable.

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 82073370, 82272794

analysis of the combination of immunotherapy and RT. We summarized the preclinical mechanisms through which RT boosts antitumor immune responses and mainly focused on the outcomes of recently updated clinical trials, including those that may not have met expectations. We investigated the optimization of the therapeutic potential of this combined strategy, including key challenges, such as fractionation and scheduling, lymph node irradiation, and toxicity. Finally, we offered insights into the prospects and challenges associated with the clinical translation of this combination therapy, providing a realistic perspective on the current state of research and potential future directions.

KEYWORDS
immunotherapy, radiotherapy, immune checkpoint inhibitor, abscopal effect, tumor microenvironment

1 | BACKGROUND

Immunotherapy, specifically immune checkpoint inhibitors (ICIs), offers a new paradigm for treating several solid tumors, including melanoma [1, 2], non-small cell lung cancer (NSCLC) [3, 4], and head and neck squamous cell carcinoma (HNSCC) [5]. However, most patients with cancer do not respond optimally to immunotherapy alone [6, 7]. Accordingly, combining immunotherapy with other established cancer treatments, including radiotherapy (RT), has garnered considerable attention [8–12].

RT, a widely used and efficacious cancer treatment modality, can enhance both localized and systemic antitumor immune responses [13, 14]. RT has evolved considerably over time, driven by advancements in diagnostic imaging and delivery techniques. A pivotal leap occurred in the development of electron linacs in the 1960s and the 1970s. The evolution of RT techniques, including intensity-modulated RT, stereotactic body RT (SBRT), image-guided RT, and proton therapy, has ushered in a new era of precision radiation for solid tumors, with lower toxicities and higher conformality of the radiation fields targeting the tumor [14–18].

The concept of radioimmunotherapy was first proposed in 2005, triggering many preclinical studies that explored the potential synergy between RT and immunotherapy [19]. However, evidence from relevant clinical trials is limited. In 2016, Bernstein *et al.* [20] introduced the definitive concept of immunotherapy and stereotactic ablative RT (ISABR). In 2018, they further advocated comprehensive irradiation of multiple lesions in the ISABR field [21] (Figure 1).

First, a secondary analysis of the KEYNOTE-001 trial (NCT01295827) provided intriguing insights into this combination strategy at the clinical trial level. The primary objective of the phase I KEYNOTE-001 trial was to assess the safety and antitumor activity of pembrolizumab (an anti-programmed cell death protein 1 [anti-PD-1] antibody) in patients with advanced NSCLC [22]. Shaverdian *et al.* [23] assessed patients with advanced NSCLC who had received RT before pembrolizumab treatment. They found that the overall survival (OS) and progression-free survival (PFS) were significantly longer in patients who had previously received RT than in those who had not, with an acceptable safety profile. This benefit was observed despite the significant interval of 9.5 months between RT and pembrolizumab treatment. Another major milestone occurred when Antonia *et al.* [24] found that in the PACIFIC trial, patients who started durvalumab (anti-programmed death-ligand 1 [anti-PD-L1] antibody) within 2 weeks after completing chemo-RT (CRT) survived longer than those who started durvalumab at 4 weeks. The PACIFIC trial, a randomized phase III trial (NCT02125461), enrolled patients with stage III unresectable NSCLC who received at least 2 cycles of platinum-based CRT. These patients were then assigned to receive durvalumab or placebo. This trial demonstrated improved OS and PFS in patients with NSCLC receiving durvalumab post-CRT [24, 25]. The latest analyses demonstrated robust and sustained OS and durable PFS benefits [26]. PACIFIC-R (NCT03798535) is a large, real-world, retrospective study of patients who received the PACIFIC regimen. Better real-world PFS outcomes were also observed among patients who received durvalumab closer to the end of RT, which is consistent with the findings from the PACIFIC trial [27]. These findings provide compelling evidence supporting the potential of RT to elicit a systemic antitumor immune response, inducing an abscopal effect. However, certain factors, including PD-1/PD-L1, impede RT-induced

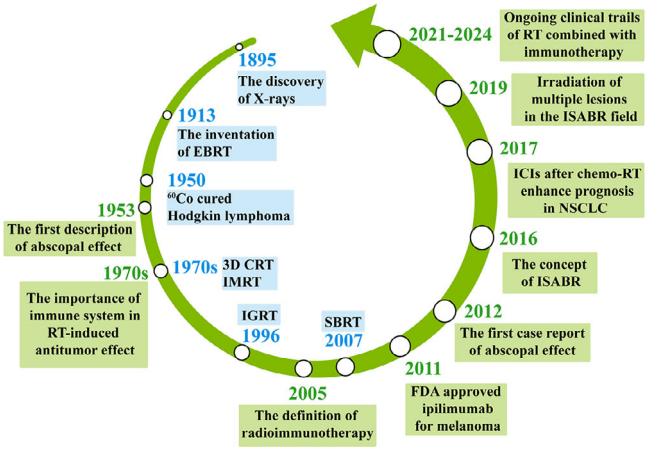

FIGURE 1 Timeline depicting important events in the development of the combination of RT and immunotherapy. Abbreviations: ICI, immune checkpoint inhibitor; IMRT, intensity-modulated radiotherapy; ISABR, immunotherapy and stereotactic ablative RT; NSCLC, non-small cell lung cancer; RT, radiotherapy.

abscopal effects, highlighting the role of ICIs in enhancing the efficacy of RT.

The purpose of this review is to provide a comprehensive and balanced examination of the combination of RT and immunotherapy in cancer treatment. We aim to present an overview of the numerous clinical trials, such as the SPRINT, DOLPHIN, PEMBRO-RT, and MDACC trials, which have released their findings in the past five years. Our goal is to shed light on the successes and setbacks of these trials, highlighting the need for a nuanced understanding of this combination therapy. In addition to summarizing the preclinical mechanisms that enhance antitumor immune responses through RT, our objective extends to exploring the potential optimization of this combined strategy, including challenges such as fractionation and scheduling, lymph node irradiation, and toxicity management. Ultimately, this review seeks to provide insights into the potential and hurdles of translating this combination therapy into clinical practice, offering a realistic view of the current state of research and possible future directions.

2 | MECHANISMS AND PRECLINICAL EVIDENCE

Several reviews have discussed the preclinical mechanisms of synergy between RT and immunotherapy [28–30]. In this section, we present an updated summary of recent preclinical studies on the impact of RT on the immune system via in situ vaccination and immune reprogramming.

2.1 | In situ vaccination

The immune mechanisms triggered by RT encompass three essential processes: immunogenic cell death and arousal of antigen-presenting cells, T cell priming in lymph nodes, and effector T cells homing to tumors [31, 32] (Figure 2). RT-damaged tumor cells release various tumor-associated antigens and damage-associated molecular patterns (DAMPs), including high-mobility group box 1 [33, 34] and adenosine triphosphate [35, 36]. Increased DAMPs activate dendritic cells (DCs) and trigger the MyD88 pathway, inducing a cascade of cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-8 [37, 38]. Furthermore, RT enhances the expression of calreticulin on the cell surface, acting as an "eat me" signal [39–41], and upregulates the expression of major histocompatibility complex (MHC) class I on tumor cells [42, 43]. RT enhances antigen cross-presentation within draining lymph nodes (DLNs) [43, 44]. During this process, activated DCs migrate to DLNs, where they present antigens to T cells [45]. After education, T cells, mainly $CD8^+$ T cells, leave the DLNs and circulate throughout the body, patrol for tumor antigens, and target both irradiated and non-irradiated tumor deposits, thereby promoting the regression of distant tumors, an intriguing phenomenon known as the abscopal response [46–49].

Cellular responses after RT are intricate and multifaceted, involving various signaling pathways that affect immune system function. There is a recurring consensus that non-tumor cell stimulator of interferon genes (STING) is a crucial factor [50, 51] (Figure 3). Radiation-generated cytoplasmic double-stranded DNA fragments trigger cyclic GMP-AMP (cGAMP) synthase activation, leading to the synthesis of the secondary messenger cGAMP [52]. This, in turn, recruits TANK-binding kinase 1 and IκB kinase [53, 54], initiating the transcription of inflammatory cytokines, especially interferon-β (IFN-β) [50, 55]. Notably, Vanpouille-Box *et al.* [56] showed that RT ranging from 12 Gy to 18 Gy activates three prime repair exonuclease 1 (TREX1) within tumor cells, thereby orchestrating the degradation of radiation-induced cytoplasmic double-stranded DNA.

2.2 | Immune reprogramming

RT also induces immune reprogramming by dynamically altering the immune milieu in response to treatment [57]. This causes the release of chemokines, including C-X-C motif chemokine ligand 9 (CXCL9) [58], CXCL10 [58, 59], and CXCL16 [60, 61], leading to the infiltration and accumulation of immune cells and reprogramming of the tumor microenvironment (TME) [62–64]. DCs [46], $CD8^+$

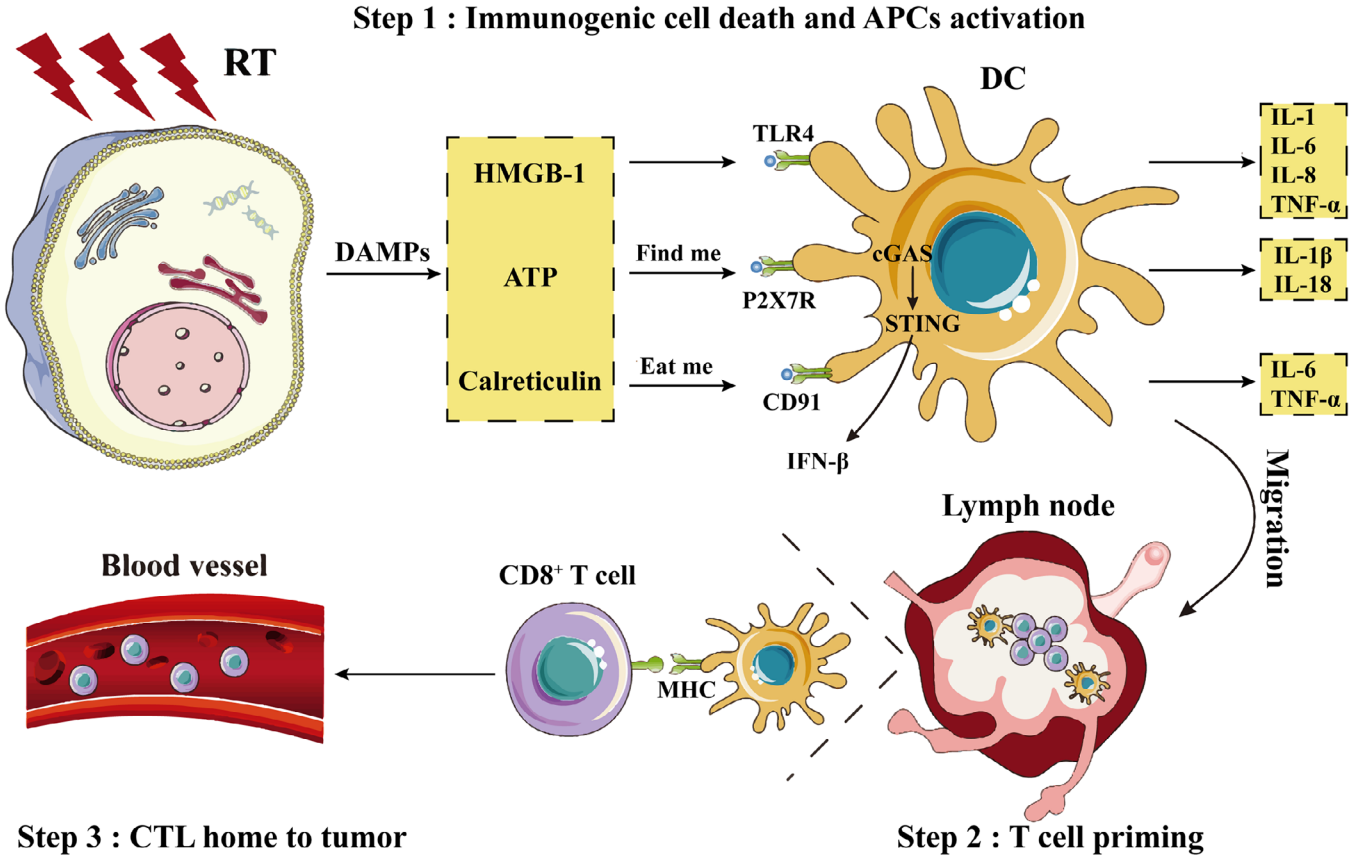

FIGURE 2 In-situ vaccination induced by RT. In-situ vaccination induced by RT encompasses three key procedures: exposure of tumor antigen and activation of APCs, T cell priming in lymph nodes, and effector T cells home to tumors. Abbreviations: APCs, antigen-presenting cells; DAMP, damage-associated molecular pattern molecules; DCs, dendritic cells; HMGB-1, high-mobility group box 1; IFN-β, interferon-β; MHC, major histocompatibility complex; RT, radiotherapy; STING, stimulator of interferon genes; TNF-α, tumor necrosis factor-α;.

T cells [65], natural killer (NK) cells [66], as well as regulatory T cells (Tregs) [67, 68] and myeloid-derived suppressor cells (MDSCs) [69], are involved in this process (Figure 4).

Immune cells exhibit differential sensitivities to radiation. For instance, immature DCs can tolerate radiation doses of 10 Gy to 30 Gy, while retaining their viability and functionality. However, mature DCs, which are crucial for immune activation, may be more radiation-sensitive [70]. Tregs are more resistant to RT than other lymphocytes [71, 72]. Recently, irradiated DCs were found to decrease the secretion of IL-12 and IL-23 cytokines, a reduction, in turn, mitigated by irradiated fibroblasts [73].

Significant $CD4^+$ T helper 1 and $CD8^+$ T cytotoxic 1 polarization was observed in tumor DLNs after RT [74]. To delve deeper into the underlying potentiation of RT and ICIs, Rudqvist *et al.* [75] identified the separate contributions of each therapy (RT and anti-cytotoxic T-lymphocyte-associated antigen 4 [anti-CTLA-4] antibody) to the T cell population. They found that the anti-CTLA-4 antibody expanded $CD4^+$ T helper 1 cells and RT expanded exhausted $CD8^+$ T cells. However, in the combination group, Tregs were reduced while CD8 effector memory, early activation, and precursor exhausted T cells were expanded compared to those in the control and monotherapy groups.

NK cells are cytotoxic innate lymphoid cells essential for the innate immunosurveillance of tumors [76, 77]. NK cells were activated by irradiated tumor cells and could regulate the response to RT and CTLA-4 blockade [66, 78]. Combining RT with the adoptive transfer of NK cells has been shown to prolong survival compared with that of RT alone [79].

Tumor-associated macrophages (TAMs) are the most abundant tumor-infiltrating lymphocytes in the TME [80–83]. TAMs are phenotypically and functionally diverse and can be broadly divided into two types: pro-inflammatory M1 and anti-inflammatory M2 macrophages [84–87]. RT can shift macrophage differentiation to the M1 phenotype, indirectly increasing tumor infiltrating lymphocytes (TIL) frequency [88, 89]. Moreover, depletion of TAMs can reverse immunosuppression and promote RT efficacy [90].

Tregs, characterized by high forkhead box protein P3 (Foxp3) and CD25 expression, inhibit antitumor

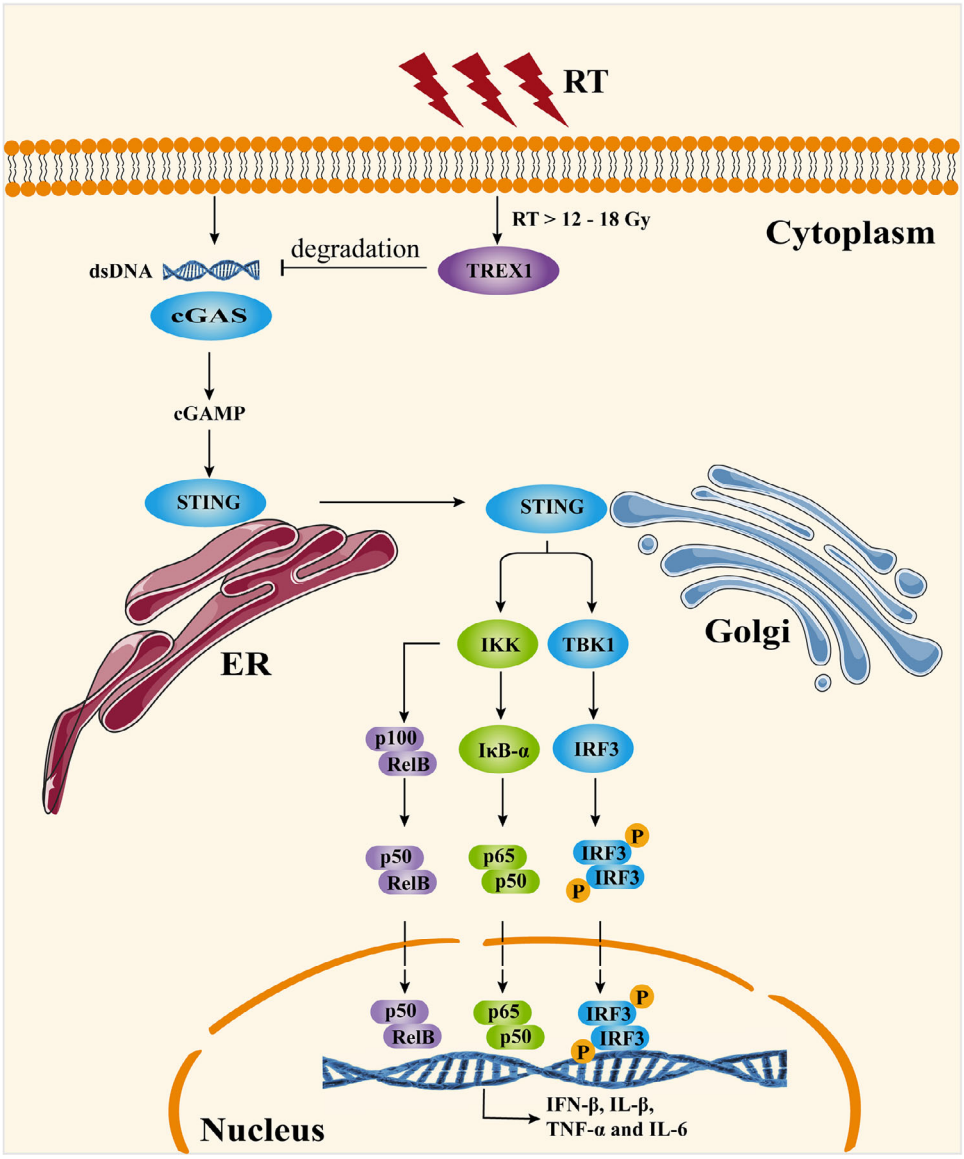

FIGURE 3 The mechanism of radiation-induced activation of the cGAS-STING pathway. Radiation-generated cytoplasmic dsDNA fragments trigger cGAS activation. Then, cGAS dimerizes and synthesizes the dinucleotide secondary messenger cGAMP, which binds to the STING at the ER. STING oligomerize and translocate to the Golgi, which involves in COP complexes. In the ER-Golgi intermediate compartment, STING recruits TBK1 and IKK. Together with STING, TBK1 is allowed to co-activate the IRF3 by phosphorylation. The phosphorylated IRF3 polymerizes and translocate to the nucleus to induce the expression of IFN-β, which are crucial for therapeutic responses to RT in immune cells. In addition, IKK activates NF-κB pathway and subsequently promotes transcription of inflammatory cytokines IL-6, IFN-β, TNF-α, and IL-1β. Abbreviations: IFN-β, interferon-β; RT, radiotherapy; STING, stimulator of interferon genes; TNF-α, tumor necrosis factor-α; TREX1, three prime repair exonuclease 1.

immunity, thereby promoting tumor development [91–93]. Different doses of RT can increase the expression of CTLA-4 on Tregs as well as the level of transforming growth factor-β (TGF-β) secreted by Tregs [94]. Moreover, in a murine model of HNSCC, RT upregulated C-C motif chemokine 2 (CCL2) chemokine production in tumor cells, resulting in the C-C chemokine receptor type 2 (CCR2)-dependent accumulation of $CCR2^{+}$ Tregs. This reduces the efficacy of RT [95]. Treg depletion combined with RT can significantly enhance immune-promoting effects, as well as reduce tumor burden and improve OS [44, 96, 97].

MDSCs are a cluster of cells with immunosuppressive effects that are classified into 2 distinct subsets: polymorphonuclear and monocytic MDSCs [98–100]. RT induces MDSC expansion and recruitment in murine models and humans [69]. Interestingly, a transient significant increase in the percentage of MDSCs was observed 3 days after RT, which then decreased at day 14 after RT [101]. The upregulation of CCL2, CCL7, and CCL12 after high-dose

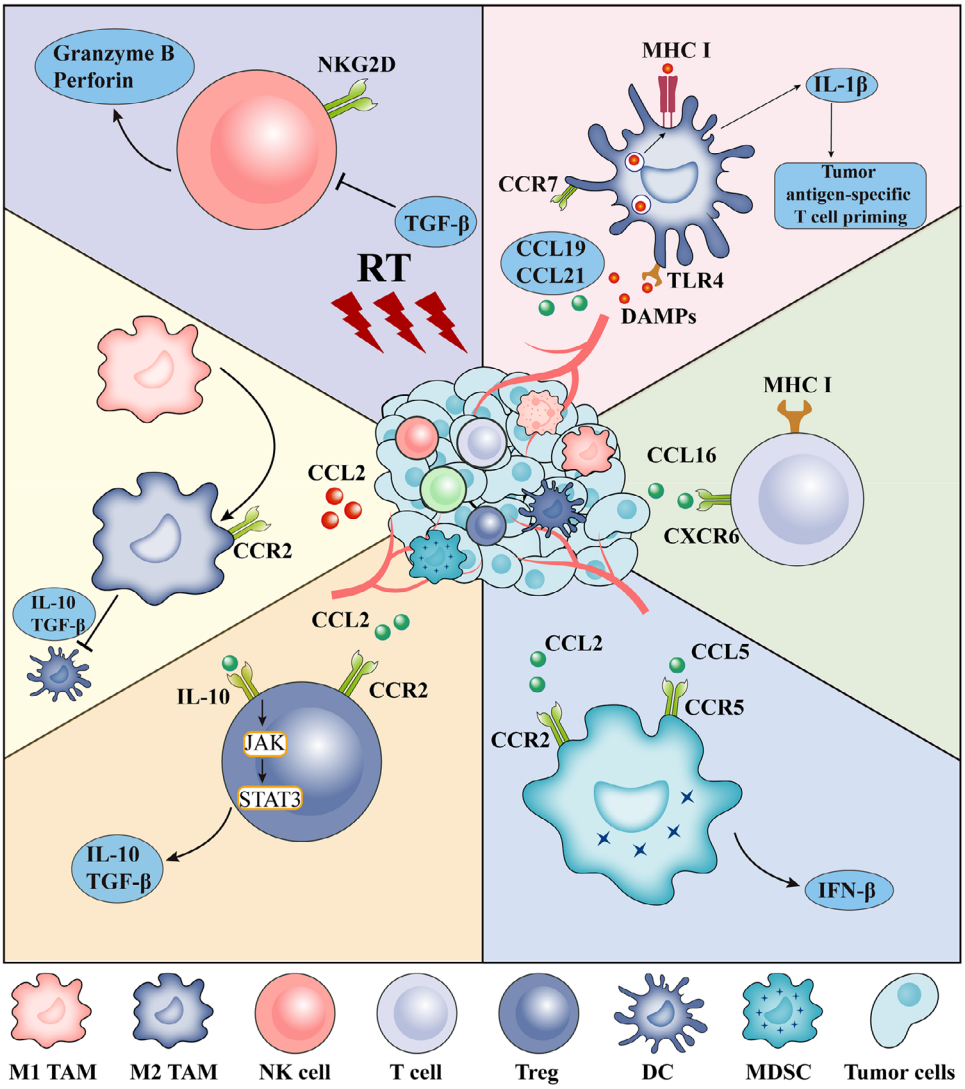

FIGURE 4 RT reprogrammed the tumor microenvironment. RT induces the upregulation of MHC class I and NK2GD, thereby promoting a potent cytotoxic response from $CD8^+$ T cells and NK cells. RT on DCs increases the expression of CCL19 and CCL21 and mediate migration of DCs. RT induced macrophage differentiation into M2 phenotype. RT increased Tregs through release of adenosine by tumor cells as well IL-10. Moreover, RT recruited MDSCs via the CCR2 pathway. Abbreviations: CCL, C-C motif chemokine; CCR, C-C chemokine receptor type; DC, dendritic cell; IFN-β, interferon-β; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK cell, natural killer cell; RT, radiotherapy; TAM, tumor-associated macrophage; TGF-β, transforming growth factor-β; Treg, regulatory T cell.

radiation (20 Gy) led to the accumulation of $CCR2^+$ MDSC in the TME [102]. The CCR2 blockade abrogates RT-induced MDSCs [102, 103]. A recent study found that RT-induced YT521B homology domain family 2 (YTHDF2) expression and YTHDF2 deficiency reversed the accumulation of MDSC following local RT, improving the effects of combined RT and/or anti-PD-L1 treatment [104].

In summary, while RT-recruited immunosuppressive cells can potentially hinder immune-stimulatory responses, it has been observed that RT can ultimately increase the effector-to-suppressor cell ratio in the TME [33]. This, combined with the upregulation of PD-L1 expression induced by RT, suggests that combining RT with ICIs could be a promising strategy for treating solid tumors [105–108] (Table 1).

3 | EVIDENCE FROM CLINICAL TRIALS

Previous case reports and limited clinical trials have demonstrated promising results when combining RT with immunotherapy [109–112]. Despite the recent disclosure of the results of several clinical trials, the future of this field remains uncertain. SBRT, also known as SABR, is the most commonly used treatment in clinical trials [113]. In this section, we discussed the results of clinical trials and

TABLE 1 Preclinical studies of RT in combination with immunotherapy.

Preclinical study	Tumor model	RT	Immunotherapy	Results
Chen *et al.*, 2021 [182]	Lewis lung carcinoma	4 fractions of 10 Gy	anti-PD-L1	Suppressed the tumor growth, improved survival, and prolonged immune memory
Hong *et al.*, 2020 [183]	MFC gastric cancer	3 fractions of 5 Gy	anti-PD-1	Improved antitumor activities in RT-insensitive tumor models
Philippou *et al.*, 2020 [184]	TRAMP-C1 and MyC-CaP prostate cancer	3 fractions of 5 Gy	anti-PD-L1	Tumor growth delay and immune cell changes
Grapin *et al.*, 2019 [185]	Subcutaneous CT26 colorectal carcinoma	3 fractions of 8 Gy, 2 fractions of 18 Gy and 1 fraction of 16.4 Gy	anti-PD-L1, anti-TIGIT	3 fractions of 8 Gy were the most effective protocol
Oweida *et al.*, 2018 [186]	MOC2 and LY2 squamous cell carcinoma	1 fraction of 20 Gy, 3 fractions of 8 Gy	anti-PD-L1, anti-TIM-3	Targeting Tregs enhances therapeutic response to RT and dual immune checkpoint blockade
Rodriguez-Ruiz *et al.*, 2017 [187]	Subcutaneous MC38 colon adenocarcinoma	3 fractions of 8 Gy	anti-PD1, anti-CD137 or both	Brachytherapy with immunotherapy can potentiate the abscopal effect
Young *et al.*, 2016 [188]	Subcutaneous CT26 colorectal carcinoma	1 fraction of 20 Gy	anti-CTLA-4 and anti-TNFRSF4	Ideal timing of RT is dependent on the mechanism of action of the respective immunotherapy utilized
Hao *et al.*, 2016 [189]	Subcutaneous LLC	1 fraction of 6 Gy	anti-CD40	RT combined with anti-CD40 boosts the abscopal effect
Habets *et al.*, 2016 [190]	Subcutaneous 67NR mammary carcinoma	3 fractions of 8 Gy	Flt3L	HFRT with Flt3L induces abscopal effect
Twyman-Saint *et al.*, 2015 [191]	Subcutaneous TSA and B16-F10	3 fractions of 8 Gy or 1 fraction of 20 Gy	anti-CTLA-4, anti-PD-1, and anti-PD-L1	Anti-CTLA-4 decreased Tregs, anti-PD-L1 reinvigorates exhausted T cells, and RT increases the TCR repertoire
Deng *et al.*, 2014 [105]	Subcutaneous TUBO mammary carcinoma and MC38	1 fraction of 12 Gy	anti-PD-L1	Increased T-cell infiltration boosts abscopal effect
Lee *et al.*, 2009 [45]	Subcutaneous 4T1 and B16-CCR7	2 fractions of 12 Gy	TNFSF14	Increased abscopal effect was $CD8^+$ T cell-mediated
Dewan *et al.*, 2009 [192]	Subcutaneous 4T1 and MC38	5 fractions of 6 Gy, 3 fractions of 8 Gy, or 1 fraction of 20 Gy	anti-CTLA-4	Fractionated but no single fraction RT with immunotherapy induced abscopal effect
Demaria *et al.*, 2005 [193]	Subcutaneous 4T1 mammary carcinoma	2 fractions of 12 Gy	anti-CTLA-4	A promising new strategy against poorly immunogenic metastatic cancers
Demaria *et al.*, 2004 [194]	Subcutaneous 67NR	1 fraction of 2-6 Gy	Flt3L	Synergism through T cell-mediated abscopal effect
Chakravarty *et al.*, 1999 [195]	Subcutaneous LLC	60 Gy	Flt3L	Improved survival and reduced pulmonary metastases

Abbreviations: CTLA-4, cytotoxic T-lymphocyte associated protein 4; Flt3L, Flt3 ligand; HFRT, hypofractionated radiotherapy; LLC, Lewis lung carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RT, radiation therapy; TCR, T cell receptor; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; TIM-3, T cell immunoglobulin and mucin domain-3; TNFRSF4, TNF receptor superfamily member 4; Treg, regulatory T cell.

findings revealed over the past five years, focusing primarily on NSCLC, where the most promising results have been observed. We also summarized the relevant clinical trials combining RT with ICIs, with a predominant emphasis on NSCLC (Table 2) and other solid tumors (Table 3).

3.1 | Early-stage NSCLC

The RTOG 0236 trial showed that SBRT achieved a high rate of tumor control in patients with medically inoperable early-stage NSCLC [114]. These patients are typically treated with definitive SBRT as the standard of care [115]. However, a longer follow-up period revealed additional cancer recurrences [116, 117]. Preclinical evidence suggests that ICIs combined with SBRT may facilitate preoperative immunotherapy without compromising antitumor efficacy, making it a safer option for neoadjuvant therapy [118].

An open-label phase II trial (NCT02904954) compared durvalumab alone with durvalumab plus SBRT (3 × 8 Gy) for early-stage NSCLC [119]. Major pathological response (MPR) rates were significantly higher in the durvalumab plus SBRT group (16/30 patients) than in the durvalumab alone group (2/30 patients). Notably, half of the patients in the dual therapy group with MPR showed complete pathological response [119].

A recent open-label phase II trial (NCT03110978) evaluated the efficacy and safety of SBRT alone and in combination with nivolumab for early-stage NSCLC. Compared with that of the SBRT group, the combination therapy group showed significantly improved four-year event-free survival with tolerable toxicity [120]. ISABR (NCT03148327), a multicenter prospective clinical trial, recently reported the safety and efficacy of the combination of SBRT and durvalumab in 18 patients [121]. These results suggest that pulmonary toxicity risk is the greatest concern for combination therapy [121].

3.2 | Oligometastases

The concept of an oligometastatic state was first postulated in 1995 [122]. This hypothesis posits that metastases may be limited to specific organs in limited numbers [123], implying potential curability with localized interventions, including RT or surgery [124]. Earlier evidence supports the safety and efficacy of SBRT for oligometastases [125]. In limited metastatic NSCLC, SBRT before maintenance chemotherapy significantly improved PFS compared with maintenance chemotherapy alone [126]. The SABR-COMET phase II trial showed that SBRT improved OS [127].

Harnessing the innate and adaptive immunity is vital for restricting metastatic development [128–130]. Pitroda *et al.* [131] identified that the upregulation of immune-related genes in colorectal liver metastases was associated with better clinical outcomes. Accordingly, the integration of immunotherapy with SBRT has been proposed for oligometastases [132] (Table 4). Luke *et al.* [133] conducted a phase I trial and found that pembrolizumab and SBRT combination therapy had an acceptable safety profile. A subsequent clinical study (NCT02316002) showed improved PFS with reduced quality of life after SBRT for oligometastatic NSCLC [134].

The results from a randomized phase II trial have established the use of SBRT to all lesions, becoming the standard of care for patients with oligometastatic NSCLC [135]. A multicenter prospective observational study aimed to determine whether concomitant anti-PD-1 and SABR could enhance tumor response in metastatic NSCLC and melanoma. In this study, all patients received concurrent pembrolizumab or nivolumab and SABR to 1 to 5 lesions, with the anti-PD-1 treatment continuing until further progression, unacceptable toxicity, or a medical/patient decision to discontinue. The objective response rate (ORR) was 42%, and the median PFS was 14.2 months [136]. This approach achieved high response rates and extended the clinical benefits of immunotherapy by delaying further progression and developing a new systemic therapy.

3.3 | Locally advanced (LA)-NSCLC

Approximately one-third of patients with NSCLC are initially diagnosed with LA disease [137]. Based on the finding of the PACIFIC trial [24, 25], concurrent CRT (cCRT) followed by consolidation durvalumab (the PACIFIC regime) became the standard of care for patients with LA-NSCLC. With updated suboptimal 5-year OS and PFS rates [26], novel treatment strategies are under investigation to improve clinical outcomes. One such approach was the GEMSTONE-301 phase III trial (NCT03728556) [138] and the PACIFIC-6 phase II trial (NCT03693300) [139]. Both trials demonstrated that ICI after sequential CRT (sCRT) is an effective consolidation therapy for LA-NSCLC, suggesting that sCRT followed by ICI could be an alternative for patients unsuitable for the PACIFIC regimen [140].

Trials exploring the use of ICIs concurrently with cCRT or sCRT have also been conducted. KEYNOTE-799 is a nonrandomized phase II trial of pembrolizumab concurrent with cCRT as the initial therapy for the treatment of LA-NSCLC, with an ORR of 70.5% [141]. The PACIFIC-2 trial (NCT03519971) randomized patients to receive durvalumab or a placebo concurrently with CRT. On November 14, 2023, the news that durvalumab administered

TABLE 2 Clinical trials combining RT with immunotherapy in NSCLC.

Condition	NCT number	Status	Phase	Immunotherapy	RT (dose and fractionation)	Timing and sequencing
Early-stage NSCLC	NCT03383302	Unknown	Phase I/II	Nivolumab	SBRT (N/A)	RT prior to immunotherapy
Early-stage NSCLC	NCT04271384	Recruiting	Phase II	Nivolumab	SBRT (N/A)	Concurrent
Stage I NSCLC	NCT03446547	Unknown	Phase II	Durvalumab	SBRT (N/A)	RT prior to immunotherapy
Stage I NSCLC	NCT04944173	Not yet recruiting	Phase II	Durvalumab	SBRT (N/A)	Concurrent
Stage I-II NSCLC	NCT03383302	Unknown	Phase I/II	Nivolumab	SBRT (N/A)	RT prior to immunotherapy
Stage I-IIA NSCLC	NCT03110978	Active, not recruiting	Phase II	Nivolumab	SBRT (N/A)	Concurrent
Stage III NSCLC	NCT05157542	Recruiting	Phase I	Durvalumab	Low dose RT (N/A)	Concurrent
Stage II-III NSCLC	NCT04310020	Recruiting	Phase II	Atezolizumab	HFRT (N/A)	RT prior to immunotherapy
Metastatic NSCLC	NCT03168464	Completed	Phase I/II	Ipilimumab/nivolumab	SBRT (30 Gy in 6 fractions)	Concurrent
Stage IV NSCLC	NCT01860430	Completed	Phase I	Pembrolizumab	Palliative EBRT (N/A)	Concurrent
Stage IV NSCLC	NCT02303990	Completed	Phase I	Pembrolizumab	SBRT (N/A)	Concurrent
Locally advanced or metastatic NSCLC	NCT05111197	Recruiting	Phase III	anti-PD-1 or anti-PD-L1	SBRT (24 Gy in 3 fractions)	Concurrent
Advanced NSCLC	NCT02839265	Completed	Phase II	FLT3 ligand (CDX-301)	SBRT (N/A)	Concurrent
Advanced NSCLC	NCT04491084	Recruiting	Phase I/II	FLT3 ligand (CDX-301) and anti-CD40 antibody (CDX-1140)	SBRT (N/A)	Concurrent
Metastatic NSCLC	NCT03825510	Completed	Phase II	Nivolumab/Pembrolizumab	SBRT (N/A)	RT prior to immunotherapy
Stage III NSCLC	NCT04577638	Active, not recruiting	Phase II	Nivolumab	IMRT (N/A)	Concurrent
Stage IV NSCLC	NCT03867175	Active, not recruiting	Phase III	Pembrolizumab	SBRT (N/A)	Concurrent
Stage IV NSCLC	NCT02608385	Active, not recruiting	Phase I	Pembrolizumab	SBRT (N/A)	Concurrent

(Continues)

TABLE 2 (Continued)

Condition	NCT number	Status	Phase	Immunotherapy	RT (dose and fractionation)	Timing and sequencing
Stage IV NSCLC	NCT02221739	Completed	Phase I/II	Ipilimumab	IMRT (30 Gy in 5 fractions)	Concurrent
Metastatic NSCLC	NCT03224871	Completed	Phase I	IL-2	HFRT (N/A)	Concurrent
NSCLC	NCT03217071	Completed	Phase II	Pembrolizumab	SBRT (a single 12 Gy dose)	Immunotherapy prior to RT
Metastatic NSCLC	NCT02463994	Completed	Early phase I	MPDL3280A (Anti-PD-L1)	IMRT (N/A)	RT prior to immunotherapy
Stage IV NSCLC	NCT03812549	Completed	Phase I	Sintilimab (Anti-PD-1)	SBRT (N/A)	Immunotherapy prior to RT
Stage IIIb or Stage IV NSCLC	NCT00879866	Completed	Phase I	EMD 521873 (immunocytokine)	RT (20 Gy in 5 fractions)	RT prior to immunotherapy
NSCLC	NCT02221739	Completed	Phase I/II	Ipilimumab	IMRT (N/A)	Concurrent
Metastatic NSCLC	NCT03158883	Completed	Early phase I	Avelumab	SBRT (N/A)	N/A
Stage IIIa/b NSCLC	NCT02434081	Completed	Phase II	Nivolumab	RT (66 Gy in 33 fractions)	Concurrent
Advanced NSCLC (PEMBRO-RT)	NCT02492568	Completed	Phase II	Pembrolizumab	SBRT (24 Gy in 3 fractions)	RT prior to Immunotherapy
Stage IV NSCLC	NCT04929041	Recruiting	Phase II/III	ICIs	SBRT (N/A)	Concurrent
Stage IV NSCLC	NCT03223155	Active, not recruiting	Phase I	Ipilimumab/nivolumab	SBRT (N/A)	Concurrent and sequential
Metastatic colorectal cancer or NSCLC	NCT02888743	Active, not recruiting	Phase II	Tremelimumab and durvalumab	High/low dose RT (N/A)	Immunotherapy prior to RT
Metastatic or locally advanced NSCLC	NCT05000710	Recruiting	Phase II	Tremelimumab and durvalumab	Low dose RT (N/A)	Concurrent
NSCLC with brain metastases	NCT04889066	Not yet recruiting	Phase II	Durvalumab	SBRT (N/A)	Concurrent
NSCLC	NCT02444741	Active, not recruiting	Phase I/II	Pembrolizumab	SBRT (N/A) or conventional RT (N/A)	Concurrent
NSCLC (KEYNOTE-799)	NCT03631784	Active, not recruiting	Phase II	Pembrolizumab	RT (60 Gy in 30 daily fractions)	Concurrent
Stage II/III NSCLC	NCT04013542	Recruiting	Phase I	Ipilimumab and nivolumab	RT (N/A)	Concurrent
Stage IV NSCLC	NCT03705403	Recruiting	Phase II	L19-IL2	SBRT (N/A)	Concurrent
Metastatic NSCLC	NCT05034055	Not yet recruiting	Phase II	Atezolizumab/tiragolumab	SBRT (N/A)	RT prior to immunotherapy

Abbreviations: SBRT, stereotactic body radiation therapy; RT, radiation therapy; EBRT, external beam radiation therapy; NSCLC, non-small cell lung cancer; IMRT, intensity modulated radiation therapy; L19-IL2, human recombinant scFv fragment directed against fibronectin containing extra domain, designated L19, combined with the pro-inflammatory interleukin-2; CIRT, carbon ion radiotherapy; HFRT, hypofractionated radiotherapy; HDCRT, high-dose conformal radiotherapy; ICI, immune checkpoint inhibitor; N/A, not applicable.

TABLE 3 Clinical trials about the combination of RT and immunotherapy in other solid tumors.

Condition	NCT number	Status	Phase	Immunotherapy	RT (dose and fractionation)	Timing and sequencing
Metastatic castration-resistant prostate cancer	NCT01807065	Completed	Phase II	Sipuleucel-T	SBRT (N/A)	RT prior to immunotherapy
Metastatic castration-resistant prostate cancer	NCT01818986	Completed	Phase II	Sipuleucel-T	SBRT (N/A)	Concurrent
Glioblastoma	NCT02313272	Completed	Phase I/II	Pembrolizumab	EBRT (N/A)	Concurrent
Glioblastoma	NCT02968940	Completed	Phase II	Avelumab	HFRT (30 Gy in 5 fractions)	N/A
Advanced melanoma	NCT01497808	Completed	Phase I	Ipilimumab	Palliative SBRT (N/A)	RT prior to immunotherapy
Advanced melanoma	NCT01449279	Completed	Phase I	Ipilimumab	Palliative EBRT (N/A)	Immunotherapy prior to RT
Advanced melanoma	NCT01689974	Terminated	Phase II	Ipilimumab	SBRT (30Gy in 5 fractions)	Immunotherapy starts day 4 of RT
Advanced melanoma	NCT01557114	Terminated	Phase I	Ipilimumab	EBRT (dose escalation, 9, 15, 18, 24 Gy in 3 fractions)	RT starts week 4 of immunotherapy
Advanced melanoma	NCT02406183	Completed	Phase I	Ipilimumab	SBRT (N/A)	Immunotherapy prior to RT
Melanoma with brain metastases	NCT01703507	Completed	Phase I	Ipilimumab	SBRT (N/A) or whole brain EBRT (N/A)	Concurrent
Melanoma with brain metastases	NCT02115139	Completed	Phase II	Ipilimumab	Whole brain EBRT (30 Gy in 10 fractions)	Concurrent
Melanoma with brain metastases	NCT02097732	Terminated	Phase II	Ipilimumab	SBRT (N/A)	Immunotherapy prior to RT
Stage III-IVb HNSCC	NCT01935921	Completed	Phase I	Ipilimumab	IMRT (N/A)	Concurrent
HNSCC	NCT04220775	Completed	Phase I/II	Bintrafusp alfa	SBRT (N/A)	Immunotherapy prior to RT
HNSCC	NCT02684253	Completed	Phase II	Nivolumab	SBRT (27 Gy in 3 fractions)	Concurrent
Metastatic clear cell renal cell carcinoma	NCT01896271	Completed	Phase II	IL-2 (proleukin)	SBRT (N/A)	Concurrent
Renal cell carcinoma	NCT03065179	Completed	Phase II	Nivolumab/ipilimumab	SBRT (N/A)	Concurrent
Metastatic urothelial cancer	NCT02826564	Completed	Phase I	Pembrolizumab	SBRT (N/A)	Concurrent and sequential
Soft tissue sarcoma	NCT01347034	Completed	Phase II	Autologous DC intra-tumoral vaccination	EBRT (N/A)	Concurrent

(Continues)

TABLE 3 (Continued)

Condition	NCT number	Status	Phase	Immunotherapy	RT (dose and fractionation)	Timing and sequencing
Stage IV soft tissue sarcoma	NCT02180698	Completed	Phase I	TLR4	Palliative EBRT (N/A)	Concurrent
Metastatic breast cancer	NCT01862900	Completed	Phase I	MEDI6469 (anti-OX40)	SBRT (3 dose escalation cohorts of 15 Gy, 20 Gy or 25 Gy to liver or lung metastases)	Concurrent
Metastatic breast cancer	NCT01421017	Completed	Phase I/II	TLR7 imiquimod	SBRT (6 Gy in 5 fractions)	Concurrent
Advanced solid tumors with liver and lung metastases	NCT02239900	Completed	Phase I	Ipilimumab	SBRT (50 Gy in 4 fractions to 1-4 lesion[s])	Immunotherapy prior to RT
Recurrent or metastatic solid tumors	NCT02318771	Unknown	Phase I	Pembrolizumab	SBRT (N/A)	Concurrent
Metastatic colorectal cancer	NCT02437071	Active, not recruiting	Phase II	Pembrolizumab	IMRT (N/A)	Concurrent
Colorectal cancer with liver Metastases	NCT03101475	Completed	Phase II	Durvalumab	SBRT (10 Gy in 3 fractions)	RT starts day 8 of immunotherapy
Locally advanced rectal cancer	NCT04663763	Not yet recruiting	Phase II	Sintilimab(anti-PD-1)/capecitabine/Oxaliplatin	Shor-course RT (25 Gy in 5 fractions)	RT prior to immunotherapy
Penile cancer	NCT03686332	Active, not recruiting	Phase II	Atezolizumab	RT (33 fractions of 1.5 Gy or 1.8 Gy)	Concurrent
Metastatic anaplastic thyroid cancer	NCT03122496	Completed	Phase I	Durvalumab/tremelimumab	SBRT (27 Gy in 3 fractions)	Immunotherapy prior to RT
Solid tumors	NCT02086721	Completed	Phase I	L19-IL2 (immunocytokine)	SBRT (N/A)	Concurrent
Solid tumors	NCT05097781	Recruiting	Phase II	Anti-PD-1 antibody	RT (N/A)	N/A
Solid tumors	NCT05229614	Recruiting	Phase II	Pembrolizumab	CIRT (N/A)	Immunotherapy prior to RT
Solid tumors	NCT02239900	Completed	Phase I	Ipilimumab	SBRT (N/A)	Concurrent and sequential
Solid tumors	NCT03220854	Completed	Phase II	Anti-PD-1/PD-L1 antibody	SBRT (N/A)	N/A
Solid tumors	NCT02987166	Completed	Phase I	Pembrolizumab	HDCRT (N/A)	Concurrent and sequential
Solid tumors	NCT02474186	Completed	Phase I/II	GM-CSF	RT (35 Gy in 10 fractions)	Concurrent
Solid tumors	NCT03313804	Recruiting	Phase II	ICIs	SBRT (N/A)	Immunotherapy prior to RT

Abbreviations: CIRT, carbon ion radiotherapy; DC, dendritic cell; EBRT, external beam radiation therapy; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDCRT, high-dose conformal radiotherapy; HFRT, hypofractionated radiotherapy; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; IMRT, intensity modulated radiation therapy; L19-IL2, human recombinant scFv fragment directed against fibronectin containing extra domain, designated L19, combined with the pro-inflammatory interleukin-2; mCRPC, metastatic castration-resistant prostate cancer; N/A, not applicable; RT, radiation therapy; SBRT, stereotactic body radiation therapy.

TABLE 4 Clinical trials about the combination of RT and immunotherapy in oligometastatic.

Condition	NCT number	Status	Phase	Immunotherapy	RT (dose and fractionation)	Timing and sequencing
Melanoma	NCT01565837	Unknown	Phase II	Ipilimumab	SBRT (N/A)	Immunotherapy prior to RT
Melanoma	NCT01416831	Active, not recruiting	Phase II	IL-2	SBRT (N/A)	Concurrent
Melanoma	NCT02107755	Unknown	Phase II	Ipilimumab	SBRT (N/A)	SBRT starts 5 weeks after first dose of ipilimumab
Solid tumors	NCT05259319	Not recruiting	Phase I	Atezolizumab and tiragolumab	SBRT (24 Gy in 3 fractions)	Sequential
NSCLC	NCT03275597	Terminated	Phase I	Durvalumab and tremelimumab	SBRT (N/A)	RT prior to immunotherapy
NSCLC	NCT03965468	Active, not recruiting	Phase II	Durvalumab	SBRT (N/A)	Concurrent
NSCLC	NCT04549428	Recruiting	Phase II	Atezolizumab	RT (a single fraction of 8 Gy)	Concurrent
NSCLC	NCT04238169	Recruiting	Phase II	Toripalimab	SBRT (N/A)	Concurrent

Abbreviations: IL-2, interleukin-2; N/A, not applicable; NSCLC, non-small cell lung cancer; RT, radiation therapy; SBRT, stereotactic body radiation therapy.

concurrently with CRT failed to achieve statistical significance for PFS compared with CRT alone was announced [142]. The failure of the PACIFIC-2 trial could be attributed to several factors, including the toxicity caused by immature treatment regime. Thus, the optimal regime of RT still requires further exploration and research.

Furthermore, the induction of ICIs before CRT in patients with LA-NSCLC is currently being explored in clinical trials. The prospective AFT-16 study (NCT03102242) evaluated the safety and efficacy of atezolizumab before CRT. The primary endpoint of the disease control rate at 12 weeks was 77.4% [143]. Recently, the analysis of secondary endpoints was updated. The median PFS was 23.7 months. The median OS is not yet estimable [144]. Owing to the encouraging PFS and OS rates without unexpected safety signals, further studies are warranted. In a retrospective study, patients with LA-NSCLC received standard of care or induction ICIs, followed by standard of care. Although the OS and PFS rates between the 2 groups were similar, the induction ICIs group had a significantly lower distant metastasis rate [145].

For patients unable to complete the PACIFIC regimen due to chemotherapy-induced adverse effects (AEs), combining RT with immunotherapy can reduce toxicity while maintaining survival [146]. The SPRINT study (NCT03523702) is a prospective phase II trial that tested sequential pembrolizumab and RT. Patients with LA-NSCLC ($n = 25$) having PD-L1 tumor proportion score (TPS) $\geq 50\%$ were enrolled. The primary endpoint was PFS. The actuarial 1-year PFS rate was 74% and the actuarial 1-year OS rate was 95% [147]. The promising initial results suggest that sequential pembrolizumab and RT may be an alternative treatment approach for patients in this setting. Further clinical trials should be designed to optimize the SPRINT regimen and compare it with the standard of care. The DOLPHIN study was a nonrandomized, single-arm, phase II trial. Patients with PD-L1 positive, LA-NSCLC received RT (60 Gy) concurrently with durvalumab, followed by maintenance durvalumab therapy. The 12-month PFS rate was 72.1%, far exceeding the 28% set under the original hypothesis. The median PFS was 25.6 months and the ORR was 90.9% [148]. This study is expected to support further development of phase III clinical trials. The START-NEW-ERA study (NCT05291780) was a single-arm phase II trial that explored the efficacy of SBRT combined with immunotherapy in patients with LA-NSCLC. The median OS was 55 months [148, 149]. Early outcomes suggest that SBRT followed by ICIs may be a suitable treatment regimen for these patients. The TRADE-hypo study (NCT04351256), a prospective randomized phase II trial, addressed the safety and efficacy of durvalumab combined with either conventional (30 × 2.00 Gy) or hypofractionated (20 × 2.75 Gy) RT. The primary end point was ORR [150]. Preliminary results were showcased at the 2024 ESMO meeting. Interim futility analysis was conducted in the conventional RT arm and was positive with 11/18 patients achieving tumor response (5 stable disease, 2 progressive disease). This suggests that for patients who are not suitable for chemotherapy, a novel combination of duvalizumab and conventional chest RT could potentially be beneficial. Additional safety, efficacy, and biomarker data are expected to be provided in May 2025.

3.4 | Metastatic NSCLC

The PEMBRO-RT (NCT02492568) and MDACC (NCT02444741) trials provided solid evidence for combining RT and ICIs for metastatic NSCLC. Both trials enrolled patients with metastatic NSCLC who were randomly assigned to receive either pembrolizumab alone or SBRT. In the phase II PEMBRO-RT trial, pembrolizumab was administered within 7 days of the completion of SBRT (3 × 8 Gy). The primary endpoint of 12-weeks ORR was improved from 20% in the pembrolizumab alone arm to 50% in the pembrolizumab after RT arm [151]. Intriguingly, subgroup analyses showed the largest benefit from the addition of RT in patients with PD-L1-negative tumors, which significantly improved PFS and OS. In the phase I/II MDACC trial, SBRT was 50 Gy/4 fractions or 45 Gy/15 fractions. No significant differences in ORR or PFS were observed; however, exploratory analyses suggested that, for patients with low PD-L1 expression, a longer median PFS was observed in the ICIs plus RT group [152]. None of the trials met the preset criteria for meaningful clinical benefit owing to the small sample size. A pooled analysis showed significantly longer median PFS (9.0 vs. 4.4 months) and median OS (19.2 vs. 8.7 months) in the pembrolizumab plus RT group, with no new safety concerns [153]. Unfortunately, this pooled study could not draw conclusions regarding the optimal dose and timing of RT to induce a distant response, which should be further confirmed in specialized, large, randomized trials.

While RT combined with ICIs shows promise for NSCLC, the enhanced antitumor effect appears to be limited to other tumor types [154]. Indeed, evidence to date has shown that combination therapy has limited benefits for most patients with HNSCC. A phase II trial (NCT02684253) enrolled patients with metastatic HNSCC who were randomly assigned to receive nivolumab alone or nivolumab in combination with SBRT. Regrettably, no improvement in clinical outcomes or evidence of the abscopal effect was found [155]. In a phase II study involving 18 patients with relapsed small cell lung cancer (SCLC) (NCT02701400), durvalumab and tremelimumab were administered with or without SBRT (3 × 9 Gy). SBRT was administered as an immune sensitizer prior to ICIs treatment. However, neither OS nor PFS showed a significant difference in the two arms [156]. In a recent trial (NCT03104439) involving patients with hepatocellular carcinoma and portal vein tumor thrombus, camrelizumab and apatinib were administered with or without SBRT (36-40 Gy/6-8 Gy). Longer median OS (12.7 vs. 8.6 months) and median PFS (4.6 vs. 2.5 months) were observed in the ICIs plus SBRT group [157]. This combination regimen showed clinical benefits with an acceptable safety profile, and may be a promising first-line therapy for patients with hepatocellular carcinoma and portal vein tumor thrombus. Regarding immune desert tumors, including microsatellite-stable colorectal cancer and pancreatic ductal adenocarcinoma, despite their limited response to immunotherapy alone, a phase II trial (NCT03104439) showed that RT can enhance the immunotherapy response even in these cases [158].

Collectively, RT combined with ICIs has demonstrated encouraging outcomes in patients with NSCLC and certain solid tumors. However, many clinical studies investigating the efficacy of combining RT with ICIs have not included ICI or RT monotherapy. This omission obstructed the ability to discern a synergistic therapeutic benefit from combination therapy compared with the effects of either monotherapy independently.

4 | CHALLENGES AND CONCERNS

4.1 | Fractionation and scheduling

For decades, conventionally fractionated radiotherapy (CFRT) has typically been delivered at doses of 1.8 to 2.0 Gy per fraction, 5 days per week, for 5-8 weeks. In contrast, hypofractionated radiotherapy (HFRT) delivers large doses in one-fifth fractions and is increasingly used in clinical practice. The most prominent example of an HFRT is SBRT. Biological differences between SBRT and CFRT exist [159]. Low-dose irradiation with a single dose (0.5-1.0 Gy) has been suggested to modulate the TME and activate immune responses [88, 160, 161]. Low-dose HFRT refers to a higher dose per fraction but a lower total dose of radiation for cancer treatment, both used in preclinical models [88] and clinical trials [162, 163].

Preclinical studies have emphasized the fractionation and scheduling of RT with ICIs to establish a long-lasting antitumor immune response [164, 165]. The optimal regimen of RT combined with ICIs to maximize the antitumor immune response remains controversial [166]. Recent clinical trials have evaluated the safety and effectiveness of HFRT and low-dose hypofractionated radiotherapy (LDHRT) in combination with ICIs. However, in patients with microsatellite stable (MSS) colorectal cancer, the abscopal effect was not observed in either radiation regime, and the median PFS and OS were limited [167]. A randomized study (NCT02888743) in 2022 evaluated ICIs combined with LDFRT or HFRT in patients with metastatic NSCLC [168]. The study did not identify any significant benefit in ORR for either the LDFRT or HFRT regimens, and no significant differences in PFS or OS were observed between the treatment arms.

A latest phase I/II clinical trial (NCT02239900) compared the administration of concurrent or sequential SBRT

with ipilimumab in patients with metastatic cancer [169, 170]. All patients received ipilimumab and were randomly assigned to 5 treatment groups based on tumor size and location. The group that received sequential ipilimumab with SBRT to the lungs showed the highest rate of clinical benefit. A recent systematic literature review sought to reach a consensus among experts on the combination of SBRT and ICIs [171]. The consensus reached was that anti-PD-L1 or anti-PD-1 treatment should continue during SBRT delivery without omission of treatment cycles and that nivolumab plus ipilimumab should not be administered on the same day as SBRT. However, in an observational cohort study of patients with early-stage NSCLC, all patients were treated with SBRT (27 Gy/1 fraction or 50 Gy/5 fractions) targeting different lung lesions [172]. This large retrospective analysis found no statistically significant differences in the 5-year OS or 5-year PFS rates, raising the question of whether the fraction and location matter. Indeed, irradiation of liver metastases in patients with NSCLC has been shown to result in stronger activation of antitumor immunity than irradiation of pulmonary metastases [170]. Several ongoing clinical trials have persistently scrutinized diverse regimens of RT combined with ICIs [173, 174]. Emerging evidence will furnish precise directives for an optimal regime.

4.2 | DLNs irradiation and dose

Notably, the total dose of the DLNs irradiation is a topic worthy of discussion. DLNs serve as the site where DCs prime antigen-specific $CD8^+$ T cells, and irradiation of lymphoid organs can result in lymphopenia [45, 175]. A study published in 2018 highlighted that irradiation of the DLN impeded adaptive immune responses and attenuated the efficacy of SBRT and ICIs [67]. A concept termed lymphocyte-sparing RT has been proposed that advocates the sparing of lymphocytes whenever possible [176]. Therefore, precautionary irradiation of the DLNs is recommended [177]. A nonrandomized phase II trial (NCT01463423) enrolled patients into 3 groups based on the tumor stage. The results suggest that individual doses and fractionation of SBRT, including doses lower than those routinely administered, are associated with local tumor control [178]. Therefore, individualized dosing should be considered in future studies.

4.3 | Toxicity

Pneumonitis and radiation pneumonitis are the most common AEs associated with the administration of CRT [141]. The overall incidence of pneumonitis in the PACIFIC trial was 33.9% [25, 27]. In real-world studies, the incidences of all-grade and grade ≥3 pneumonitis were 35% and 6%, respectively [179]. The incidence of pneumonitis varies with race and age [146, 179]. The MDACC trial found that most AEs were self-limiting, and no patient in the ICI combined with SBRT group experienced grade 4 or 5 toxic effects [152]. However, another multicenter analysis demonstrated that SBRT with concurrent ICI increased the risk of grade 3 pneumonitis compared with that of SBRT alone [180]. Closer monitoring should be considered in patients who are administered ICIs and RT. Differentiating between RT-induced pneumonitis and immune-related pneumonitis is challenging [27]. Radiomics holds great promise in aiding correct diagnosis [181]. To date, evidence indicates that the observed risk of severe toxicity for SBRT plus anti-PD1/PD-L1 monotherapy is low [171], and it remains to be seen whether the combination simply increases or amplifies toxicity. In the absence of objective data showing that simultaneous administration leads to a significant increase in toxicity, RT combined with ICI is a reasonable strategy in clinical practice.

5 | CONCLUSIONS

The immune system's capacity to reject a tumor depends on the presence of neoantigens within cancer cells. RT increases the number of neoantigens via in situ vaccination. Additionally, RT reprograms the TME to foster a durable and systemic immune response. Ongoing studies have explored precision RT based on gene expression profiles to complement the precision of cancer medicine using immunotherapy.

In conclusion, the integration of RT with immunotherapy represents a paradigm shift in cancer treatment. This field awaits the results of the ongoing clinical trials. Over the past five years, promising clinical trial outcomes have been predominantly observed in NSCLC. Conversely, trials investigating other solid malignancies, including HNSCC and colorectal cancer, are limited in number, and the outcomes have been less encouraging. The inherent heterogeneity of tumors may dictate disparate responses to the combination of RT and immunotherapy. A severe limitation of ongoing clinical trials is that they are not biomarker-driven. Biomarker implementation and the identification of distinct patient subsets are priorities. However, challenges, including determining the optimal dosing, fraction, and schedule with the lowest toxicity of the combination therapy, remain. Further research is imperative to refine combination therapy and identify predictive biomarkers for the individualized treatment of solid tumors.

AUTHOR CONTRIBUTIONS

Yuze Wu drafted the manuscript and prepared the figures. Ming Yi, Mengke Niu, and Binghan Zhou helped in collecting the related literatures and participated in discussion. Kongming Wu and Qi Mei designed the review and revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (82073370 and 82272794).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ORCID

Kongming Wu https://orcid.org/0000-0003-2499-1032

REFERENCES

1. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020;17(8):807–21.
2. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
3. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823–33.
4. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–64.
5. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016;375(19):1856–67.
6. Yang K, Halima A, Chan TA. Antigen presentation in cancer - mechanisms and clinical implications for immunotherapy. Nat Rev Clin Oncol. 2023;20(9):604–23.
7. Ma W, Xue R, Zhu Z, Farrukh H, Song W, Li T, et al. Increasing cure rates of solid tumors by immune checkpoint inhibitors. Exp Hematol Oncol. 2023;12(1):10.
8. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nat Rev Drug Discov. 2019;18(3):197–218.
9. Kubli SP, Berger T, Araujo DV, Siu LL, Mak TW. Beyond immune checkpoint blockade: emerging immunological strategies. Nat Rev Drug Discov. 2021;20(12):899–919.
10. Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Mol Cancer. 2022;21(1):28.
11. Liu S, Sun Q, Ren X. Novel strategies for cancer immunotherapy: counter-immunoediting therapy. J Hematol Oncol. 2023;16(1):38.
12. Wu M, Huang Q, Xie Y, Wu X, Ma H, Zhang Y, et al. Improvement of the anticancer efficacy of PD-1/PD-L1 blockade via combination therapy and PD-L1 regulation. J Hematol Oncol. 2022;15(1):24.
13. Grassberger C, Ellsworth SG, Wilks MQ, Keane FK, Loeffler JS. Assessing the interactions between radiotherapy and antitumour immunity. Nat Rev Clin Oncol. 2019;16(12):729–45.
14. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer. 2018;18(5):313–22.
15. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol. 2017;35(1):56–62.
16. Thariat J, Hannoun-Levi JM, Sun Myint A, Vuong T, Gérard JP. Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol. 2013;10(1):52–60.
17. Bortfeld TR, Loeffler JS. Three ways to make proton therapy affordable. Nature. 2017;549(7673):451–3.
18. Yuan TZ, Zhan ZJ, Qian CN. New frontiers in proton therapy: applications in cancers. Cancer Commun (Lond). 2019;39(1):61.
19. Demaria S, Bhardwaj N, McBride WH, Formenti SC. Combining radiotherapy and immunotherapy: a revived partnership. Int J Radiat Oncol Biol Phys. 2005;63(3):655–66.
20. Bernstein MB, Krishnan S, Hodge JW, Chang JY. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? Nat Rev Clin Oncol. 2016;13(8):516–24.
21. Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. Nat Rev Clin Oncol. 2019;16(2):123–35.
22. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018–28.
23. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. The lancet oncology. 2017;18(7):895–903.
24. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342–50.
25. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919–29.
26. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2022;40(12):1301–11.

27. Girard N, Bar J, Garrido P, Garassino MC, McDonald F, Mornex F, et al. Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study. J Thorac Oncol. 2023;18(2):181–93.
28. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol. 2015;16(13):e498–509.
29. Lhuillier C, Rudqvist NP, Elemento O, Formenti SC, Demaria S. Radiation therapy and anti-tumor immunity: exposing immunogenic mutations to the immune system. Genome Med. 2019;11(1):40.
30. Herrera FG, Irving M, Kandalaft LE, Coukos G. Rational combinations of immunotherapy with radiotherapy in ovarian cancer. Lancet Oncol. 2019;20(8):e417–e33.
31. Herrera FG, Bourhis J, Coukos G. Radiotherapy combination opportunities leveraging immunity for the next oncology practice. CA Cancer J Clin. 2017;67(1):65–85.
32. Zheng X, Jin X, Ye F, Liu X, Yu B, Li Z, et al. Ferroptosis: a novel regulated cell death participating in cellular stress response, radiotherapy, and immunotherapy. Exp Hematol Oncol. 2023;12(1):65.
33. Chang MC, Chen YL, Lin HW, Chiang YC, Chang CF, Hsieh SF, et al. Irradiation Enhances Abscopal Anti-tumor Effects of Antigen-Specific Immunotherapy through Regulating Tumor Microenvironment. Mol Ther. 2018;26(2):404–19.
34. Apetoh L, Ghiringhelli F, Tesniere A, Obeid M, Ortiz C, Criollo A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med. 2007;13(9):1050–9.
35. Elliott MR, Chekeni FB, Trampont PC, Lazarowski ER, Kadl A, Walk SF, et al. Nucleotides released by apoptotic cells act as a find-me signal to promote phagocytic clearance. Nature. 2009;461(7261):282–6.
36. Bao X, Xie L. Targeting purinergic pathway to enhance radiotherapy-induced immunogenic cancer cell death. J Exp Clin Cancer Res. 2022;41(1):222.
37. Andersson U, Wang H, Palmblad K, Aveberger AC, Bloom O, Erlandsson-Harris H, et al. High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. J Exp Med. 2000;192(4):565–70.
38. Ozpiskin OM, Zhang L, Li JJ. Immune targets in the tumor microenvironment treated by radiotherapy. Theranostics. 2019;9(5):1215–31.
39. Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, Perfettini JL, et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat Med. 2007;13(1):54–61.
40. Surace L, Lysenko V, Fontana AO, Cecconi V, Janssen H, Bicvic A, et al. Complement is a central mediator of radiotherapy-induced tumor-specific immunity and clinical response. Immunity. 2015;42(4):767–77.
41. Fucikova J, Spisek R, Kroemer G, Galluzzi L. Calreticulin and cancer. Cell Res. 2021;31(1):5–16.
42. Dillon MT, Bergerhoff KF, Pedersen M, Whittock H, Crespo-Rodriguez E, Patin EC, et al. ATR Inhibition Potentiates the Radiation-induced Inflammatory Tumor Microenvironment. Clin Cancer Res. 2019;25(11):3392–403.
43. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med. 2006;203(5):1259–71.
44. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer Immunol Res. 2015;3(4):345–55.
45. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood. 2009;114(3):589–95.
46. Gupta A, Probst HC, Vuong V, Landshammer A, Muth S, Yagita H, et al. Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation. J Immunol. 2012;189(2):558–66.
47. Takeshima T, Chamoto K, Wakita D, Ohkuri T, Togashi Y, Shirato H, et al. Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy. Cancer Res. 2010;70(7):2697–706.
48. Huang Q, Wang F, Hao D, Li X, Li X, Lei T, et al. Deciphering tumor-infiltrating dendritic cells in the single-cell era. Exp Hematol Oncol. 2023;12(1):97.
49. Yu J, Sun H, Cao W, Song Y, Jiang Z. Research progress on dendritic cell vaccines in cancer immunotherapy. Exp Hematol Oncol. 2022;11(1):3.
50. Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, et al. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity. 2014;41(5):843–52.
51. Corrales L, Glickman LH, McWhirter SM, Kanne DB, Sivick KE, Katibah GE, et al. Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity. Cell Rep. 2015;11(7):1018–30.
52. Skopelja-Gardner S, An J, Elkon KB. Role of the cGAS-STING pathway in systemic and organ-specific diseases. Nat Rev Nephrol. 2022;18(9):558–72.
53. Hopfner KP, Hornung V. Molecular mechanisms and cellular functions of cGAS-STING signalling. Nat Rev Mol Cell Biol. 2020;21(9):501–21.
54. Wang Y, Luo J, Alu A, Han X, Wei Y, Wei X. cGAS-STING pathway in cancer biotherapy. Mol Cancer. 2020;19(1):136.
55. Hou Y, Liang H, Rao E, Zheng W, Huang X, Deng L, et al. Non-canonical NF-κB Antagonizes STING Sensor-Mediated DNA Sensing in Radiotherapy. Immunity. 2018;49(3):490–503.e4.
56. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat Commun. 2017;8:15618.
57. Donlon NE, Power R, Hayes C, Reynolds JV, Lysaght J. Radiotherapy, immunotherapy, and the tumour microenvironment: Turning an immunosuppressive milieu into a therapeutic opportunity. Cancer Lett. 2021;502:84–96.
58. Weichselbaum RR, Liang H, Deng L, Fu YX. Radiotherapy and immunotherapy: a beneficial liaison? Nat Rev Clin Oncol. 2017;14(6):365–79.

59. Meng Y, Mauceri HJ, Khodarev NN, Darga TE, Pitroda SP, Beckett MA, et al. Ad.Egr-TNF and local ionizing radiation suppress metastases by interferon-beta-dependent activation of antigen-specific CD8+ T cells. Mol Ther. 2010;18(5):912–20.
60. Matsumura S, Wang B, Kawashima N, Braunstein S, Badura M, Cameron TO, et al. Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. J Immunol. 2008;181(5):3099–107.
61. Matsumura S, Demaria S. Up-regulation of the pro-inflammatory chemokine CXCL16 is a common response of tumor cells to ionizing radiation. Radiat Res. 2010;173(4):418–25.
62. McLaughlin M, Patin EC, Pedersen M, Wilkins A, Dillon MT, Melcher AA, et al. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. Nat Rev Cancer. 2020;20(4):203–17.
63. Jia Q, Wang A, Yuan Y, Zhu B, Long H. Heterogeneity of the tumor immune microenvironment and its clinical relevance. Exp Hematol Oncol. 2022;11(1):24.
64. Tie Y, Tang F, Wei YQ, Wei XW. Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets. J Hematol Oncol. 2022;15(1):61.
65. Formenti SC, Rudqvist NP, Golden E, Cooper B, Wennerberg E, Lhuillier C, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med. 2018;24(12):1845–51.
66. Pilones KA, Kawashima N, Yang AM, Babb JS, Formenti SC, Demaria S. Invariant natural killer T cells regulate breast cancer response to radiation and CTLA-4 blockade. Clin Cancer Res. 2009;15(2):597–606.
67. Marciscano AE, Ghasemzadeh A, Nirschl TR, Theodros D, Kochel CM, Francica BJ, et al. Elective Nodal Irradiation Attenuates the Combinatorial Efficacy of Stereotactic Radiation Therapy and Immunotherapy. Clin Cancer Res. 2018;24(20):5058–71.
68. Price JG, Idoyaga J, Salmon H, Hogstad B, Bigarella CL, Ghaffari S, et al. CDKN1A regulates Langerhans cell survival and promotes Treg cell generation upon exposure to ionizing irradiation. Nat Immunol. 2015;16(10):1060–8.
69. Xu J, Escamilla J, Mok S, David J, Priceman S, West B, et al. CSF1R signaling blockade stanches tumor-infiltrating myeloid cells and improves the efficacy of radiotherapy in prostate cancer. Cancer Res. 2013;73(9):2782–94.
70. Merrick A, Errington F, Milward K, O'Donnell D, Harrington K, Bateman A, et al. Immunosuppressive effects of radiation on human dendritic cells: reduced IL-12 production on activation and impairment of naive T-cell priming. Br J Cancer. 2005;92(8):1450–8.
71. Balogh A, Persa E, Bogdándi EN, Benedek A, Hegyesi H, Sáfrány G, et al. The effect of ionizing radiation on the homeostasis and functional integrity of murine splenic regulatory T cells. Inflamm Res. 2013;62(2):201–12.
72. Wang M, Gou X, Wang L. Protein kinase B promotes radiation-induced regulatory T cell survival in bladder carcinoma. Scand J Immunol. 2012;76(1):70–4.
73. Malecka A, Wang Q, Shah S, Sutavani RV, Spendlove I, Ramage JM, et al. Stromal fibroblasts support dendritic cells to maintain IL-23/Th17 responses after exposure to ionizing radiation. J Leukoc Biol. 2016;100(2):381–9.
74. Battaglia A, Buzzonetti A, Martinelli E, Fanelli M, Petrillo M, Ferrandina G, et al. Selective changes in the immune profile of tumor-draining lymph nodes after different neoadjuvant chemoradiation regimens for locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2010;76(5):1546–53.
75. Rudqvist NP, Charpentier M, Lhuillier C, Wennerberg E, Spada S, Sheridan C, et al. Immunotherapy targeting different immune compartments in combination with radiation therapy induces regression of resistant tumors. Nat Commun. 2023;14(1):5146.
76. Maskalenko NA, Zhigarev D, Campbell KS. Harnessing natural killer cells for cancer immunotherapy: dispatching the first responders. Nat Rev Drug Discov. 2022;21(8):559–77.
77. Wolf NK, Kissiov DU, Raulet DH. Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. Nat Rev Immunol. 2023;23(2):90–105.
78. Kim JY, Son YO, Park SW, Bae JH, Chung JS, Kim HH, et al. Increase of NKG2D ligands and sensitivity to NK cell-mediated cytotoxicity of tumor cells by heat shock and ionizing radiation. Exp Mol Med. 2006;38(5):474–84.
79. Ames E, Canter RJ, Grossenbacher SK, Mac S, Smith RC, Monjazeb AM, et al. Enhanced targeting of stem-like solid tumor cells with radiation and natural killer cells. Oncoimmunology. 2015;4(9):e1036212.
80. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity. 2014;41(1):49–61.
81. Cassetta L, Pollard JW. A timeline of tumour-associated macrophage biology. Nat Rev Cancer. 2023;23(4):238–57.
82. Yi M, Li T, Niu M, Mei Q, Zhao B, Chu Q, et al. Exploiting innate immunity for cancer immunotherapy. Mol Cancer. 2023;22(1):187.
83. Wang L, He T, Liu J, Tai J, Wang B, Chen Z, et al. Pan-cancer analysis reveals tumor-associated macrophage communication in the tumor microenvironment. Exp Hematol Oncol. 2021;10(1):31.
84. Bied M, Ho WW, Ginhoux F, Blériot C. Roles of macrophages in tumor development: a spatiotemporal perspective. Cell Mol Immunol. 2023;20(9):983–92.
85. Pittet MJ, Michielin O, Migliorini D. Clinical relevance of tumour-associated macrophages. Nat Rev Clin Oncol. 2022;19(6):402–21.
86. Krausgruber T, Blazek K, Smallie T, Alzabin S, Lockstone H, Sahgal N, et al. IRF5 promotes inflammatory macrophage polarization and TH1-TH17 responses. Nat Immunol. 2011;12(3):231–8.
87. Zhu S, Yi M, Wu Y, Dong B, Wu K. Roles of tumor-associated macrophages in tumor progression: implications on therapeutic strategies. Exp Hematol Oncol. 2021;10(1):60.
88. Klug F, Prakash H, Huber PE, Seibel T, Bender N, Halama N, et al. Low-dose irradiation programs macrophage differentiation to an iNOS$^+$/M1 phenotype that orchestrates effective T cell immunotherapy. Cancer Cell. 2013;24(5):589–602.
89. Kordbacheh T, Honeychurch J, Blackhall F, Faivre-Finn C, Illidge T. Radiotherapy and anti-PD-1/PD-L1 combinations in lung cancer: building better translational research platforms. Ann Oncol. 2018;29(2):301–10.
90. Meng Y, Beckett MA, Liang H, Mauceri HJ, van Rooijen N, Cohen KS, et al. Blockade of tumor necrosis factor alpha

signaling in tumor-associated macrophages as a radiosensitizing strategy. Cancer Res. 2010;70(4):1534–43.
91. Raffin C, Vo LT, Bluestone JA. T(reg) cell-based therapies: challenges and perspectives. Nat Rev Immunol. 2020;20(3):158–72.
92. Togashi Y, Shitara K, Nishikawa H. Regulatory T cells in cancer immunosuppression - implications for anticancer therapy. Nat Rev Clin Oncol. 2019;16(6):356–71.
93. Goral A, Sledz M, Manda-Handzlik A, Cieloch A, Wojciechowska A, Lachota M, et al. Regulatory T cells contribute to the immunosuppressive phenotype of neutrophils in a mouse model of chronic lymphocytic leukemia. Exp Hematol Oncol. 2023;12(1):89.
94. Persa E, Balogh A, Sáfrány G, Lumniczky K. The effect of ionizing radiation on regulatory T cells in health and disease. Cancer Lett. 2015;368(2):252–61.
95. Mondini M, Loyher PL, Hamon P, Gerbé de Thoré M, Laviron M, Berthelot K, et al. CCR2-Dependent Recruitment of Tregs and Monocytes Following Radiotherapy Is Associated with TNFα-Mediated Resistance. Cancer Immunol Res. 2019;7(3):376–87.
96. Kachikwu EL, Iwamoto KS, Liao YP, DeMarco JJ, Agazaryan N, Economou JS, et al. Radiation enhances regulatory T cell representation. Int J Radiat Oncol Biol Phys. 2011;81(4):1128–35.
97. Bos PD, Plitas G, Rudra D, Lee SY, Rudensky AY. Transient regulatory T cell ablation deters oncogene-driven breast cancer and enhances radiotherapy. J Exp Med. 2013;210(11):2435–66.
98. Wu Y, Yi M, Niu M, Mei Q, Wu K. Myeloid-derived suppressor cells: an emerging target for anticancer immunotherapy. Mol Cancer. 2022;21(1):184.
99. Hegde S, Leader AM, Merad M. MDSC: Markers, development, states, and unaddressed complexity. Immunity. 2021;54(5):875–84.
100. Cheng X, Wang H, Wang Z, Zhu B, Long H. Tumor-associated myeloid cells in cancer immunotherapy. J Hematol Oncol. 2023;16(1):71.
101. Filatenkov A, Baker J, Mueller AM, Kenkel J, Ahn GO, Dutt S, et al. Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions. Clin Cancer Res. 2015;21(16):3727–39.
102. Kalbasi A, Komar C, Tooker GM, Liu M, Lee JW, Gladney WL, et al. Tumor-Derived CCL2 Mediates Resistance to Radiotherapy in Pancreatic Ductal Adenocarcinoma. Clin Cancer Res. 2017;23(1):137–48.
103. Liang H, Deng L, Hou Y, Meng X, Huang X, Rao E, et al. Host STING-dependent MDSC mobilization drives extrinsic radiation resistance. Nat Commun. 2017;8(1):1736.
104. Wang L, Dou X, Chen S, Yu X, Huang X, Zhang L, et al. YTHDF2 inhibition potentiates radiotherapy antitumor efficacy. Cancer Cell. 2023;41(7):1294–308.e8.
105. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124(2):687–95.
106. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res. 2014;74(19):5458–68.
107. Liu Z, Yu X, Xu L, Li Y, Zeng C. Current insight into the regulation of PD-L1 in cancer. Exp Hematol Oncol. 2022;11(1):44.
108. Yi M, Niu M, Xu L, Luo S, Wu K. Regulation of PD-L1 expression in the tumor microenvironment. J Hematol Oncol. 2021;14(1):10.
109. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med. 2012;366(10):925–31.
110. Hiniker SM, Chen DS, Reddy S, Chang DT, Jones JC, Mollick JA, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. Transl Oncol. 2012;5(6):404–7.
111. Karam SD, Raben D. Radioimmunotherapy for the treatment of head and neck cancer. Lancet Oncol. 2019;20(8):e404–e16.
112. Deutsch E, Chargari C, Galluzzi L, Kroemer G. Optimising efficacy and reducing toxicity of anticancer radioimmunotherapy. Lancet Oncol. 2019;20(8):e452–e63.
113. Chandra RA, Keane FK, Voncken FEM, Thomas CR, Jr. Contemporary radiotherapy: present and future. Lancet. 2021;398(10295):171–84.
114. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303(11):1070–6.
115. Chaft JE, Rimner A, Weder W, Azzoli CG, Kris MG, Cascone T. Evolution of systemic therapy for stages I-III non-metastatic non-small-cell lung cancer. Nat Rev Clin Oncol. 2021;18(9):547–57.
116. Timmerman RD, Hu C, Michalski JM, Bradley JC, Galvin J, Johnstone DW, et al. Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer. JAMA Oncol. 2018;4(9):1287–8.
117. Videtic GM, Paulus R, Singh AK, Chang JY, Parker W, Olivier KR, et al. Long-term Follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2019;103(5):1077–84.
118. Schneiders FL, Senan S. Finding the Goldilocks zone in neoadjuvant radioimmunotherapy. Nat Rev Clin Oncol. 2021;18(9):545–6.
119. Altorki NK, McGraw TE, Borczuk AC, Saxena A, Port JL, Stiles BM, et al. Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial. Lancet Oncol. 2021;22(6):824–35.
120. Chang JY, Lin SH, Dong W, Liao Z, Gandhi SJ, Gay CM, et al. Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet. 2023;402(10405):871–81.
121. Wu TC, Stube A, Felix C, Oseguera D, Romero T, Goldman J, et al. Safety and Efficacy Results From iSABR, a Phase 1 Study of Stereotactic ABlative Radiotherapy in Combination With Durvalumab for Early-Stage Medically Inoperable Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2023;117(1):118–22.
122. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10.
123. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8(6):378–82.

124. Corbin KS, Hellman S, Weichselbaum RR. Extracranial oligometastases: a subset of metastases curable with stereotactic radiotherapy. J Clin Oncol. 2013;31(11):1384–90.
125. Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic body radiotherapy for oligometastases. Lancet Oncol. 2013;14(1):e28–37.
126. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2018;4(1):e173501.
127. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051–8.
128. Angelova M, Mlecnik B, Vasaturo A, Bindea G, Fredriksen T, Lafontaine L, et al. Evolution of Metastases in Space and Time under Immune Selection. Cell. 2018;175(3):751–65.e16.
129. Mlecnik B, Bindea G, Kirilovsky A, Angell HK, Obenauf AC, Tosolini M, et al. The tumor microenvironment and Immunoscore are critical determinants of dissemination to distant metastasis. Sci Transl Med. 2016;8(327):327ra26.
130. Van den Eynde M, Mlecnik B, Bindea G, Fredriksen T, Church SE, Lafontaine L, et al. The Link between the Multiverse of Immune Microenvironments in Metastases and the Survival of Colorectal Cancer Patients. Cancer Cell. 2018;34(6):1012–26.e3.
131. Pitroda SP, Khodarev NN, Huang L, Uppal A, Wightman SC, Ganai S, et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat Commun. 2018;9(1):1793.
132. Pitroda SP, Chmura SJ, Weichselbaum RR. Integration of radiotherapy and immunotherapy for treatment of oligometastases. Lancet Oncol. 2019;20(8):e434–e42.
133. Luke JJ, Lemons JM, Karrison TG, Pitroda SP, Melotek JM, Zha Y, et al. Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors. J Clin Oncol. 2018;36(16):1611–8.
134. Bauml JM, Mick R, Ciunci C, Aggarwal C, Davis C, Evans T, et al. Pembrolizumab After Completion of Locally Ablative Therapy for Oligometastatic Non-Small Cell Lung Cancer: A Phase 2 Trial. JAMA Oncol. 2019;5(9):1283–90.
135. Gomez DR, Blumenschein GR, Jr., Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672–82.
136. Chicas-Sett R, Zafra J, Rodriguez-Abreu D, Castilla-Martinez J, Benitez G, Salas B, et al. Combination of SABR With Anti-PD-1 in Oligoprogressive Non-Small Cell Lung Cancer and Melanoma: Results of a Prospective Multicenter Observational Study. Int J Radiat Oncol Biol Phys. 2022;114(4):655–65.
137. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7–33.
138. Zhou Q, Chen M, Jiang O, Pan Y, Hu D, Lin Q, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2022;23(2):209–19.
139. Garassino MC, Mazieres J, Reck M, Chouaid C, Bischoff H, Reinmuth N, et al. Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial. J Thorac Oncol. 2022;17(12):1415–27.
140. Zhao B, Li H, Wu J, Ma W. Durvalumab After Sequential Chemoradiotherapy Is Safe for Stage III, Unresectable NSCLC: Results From Phase 2 PACIFIC-6 Trial. J Thorac Oncol. 2023;18(1):e1–e2.
141. Jabbour SK, Lee KH, Frost N, Breder V, Kowalski DM, Pollock T, et al. Pembrolizumab Plus Concurrent Chemoradiation Therapy in Patients With Unresectable, Locally Advanced, Stage III Non-Small Cell Lung Cancer: The Phase 2 KEYNOTE-799 Nonrandomized Trial. JAMA Oncol. 2021;7(9):1–9.
142. Bradley J, Sugawara S, Lee K, Ostoros G, Demirkazik A, Zemanova M, et al. LBA1 Durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: Final results from PACIFIC-2. ESMO Open. 2024;9:102986.
143. Ross HJ, Kozono DE, Urbanic JJ, Williams TM, Dufrane C, Bara I, et al. AFT-16: Phase II trial of atezolizumab before and after definitive chemoradiation (CRT) for unresectable stage III non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2020;38(15_suppl):9045.
144. Ross HJ, Kozono DE, Urbanic JJ, Williams TM, DuFrane C, Bara I, et al. AFT-16: Phase II trial of neoadjuvant and adjuvant atezolizumab and chemoradiation (CRT) for stage III non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2021;39(15_suppl):8513.
145. Yang Y, Wang J, Zhang T, Zhou Z, Wang Y, Jiang Y, et al. Efficacy and safety of definitive chemoradiotherapy with or without induction immune checkpoint inhibitors in patients with stage III non-small cell lung cancer. Front Immunol. 2023;14:1281888.
146. Stinchcombe TE, Zhang Y, Vokes EE, Schiller JH, Bradley JD, Kelly K, et al. Pooled Analysis of Individual Patient Data on Concurrent Chemoradiotherapy for Stage III Non-Small-Cell Lung Cancer in Elderly Patients Compared With Younger Patients Who Participated in US National Cancer Institute Cooperative Group Studies. J Clin Oncol. 2017;35(25):2885–92.
147. Ohri N, Jolly S, Cooper BT, Kabarriti R, Bodner WR, Klein J, et al. The Selective Personalized Radio-immunotherapy for Locally Advanced NSCLC Trial (SPRINT): Initial results. Journal of Clinical Oncology. 2022;40(16_suppl):8510.
148. Tachihara M, Tsujino K, Ishihara T, Hayashi H, Sato Y, Kurata T, et al. Durvalumab Plus Concurrent Radiotherapy for Treatment of Locally Advanced Non-Small Cell Lung Cancer: The DOLPHIN Phase 2 Nonrandomized Controlled Trial. JAMA Oncol. 2023;9(11):1505–13.
149. Arcidiacono F, Anselmo P, Casale M, Zannori C, Ragusa M, Mancioli F, et al. STereotactic Ablative RadioTherapy in NEWly Diagnosed and Recurrent Locally Advanced Non-Small Cell Lung Cancer Patients Unfit for ConcurrEnt RAdio-Chemotherapy: Early Analysis of the START-NEW-ERA Non-Randomised Phase II Trial. Int J Radiat Oncol Biol Phys. 2023;115(4):886–96.
150. Bozorgmehr F, Juergens J, Hammer-Hellmig M, Bueschenfelde CMZ, Classen J, Alt J, et al. Thoracic radiotherapy PLUS

durvalumab in elderly and/or frail NSCLC stage III patients unfit for chemotherapy: Employing optimized (hypofractionated) radiotherapy to foster durvalumab efficacy—The TRADE-hypo trial. Journal of Clinical Oncology. 2021;39(15_suppl):TPS8585-TPS.

151. Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019;5(9):1276–82.
152. Welsh J, Menon H, Chen D, Verma V, Tang C, Altan M, et al. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. J Immunother Cancer. 2020;8(2):e001001.
153. Theelen W, Chen D, Verma V, Hobbs BP, Peulen HMU, Aerts J, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respir Med. 2021;9(5):467–75.
154. Torok JA, Salama JK. Combining immunotherapy and radiotherapy for the STAR treatment. Nat Rev Clin Oncol. 2019;16(11):666–7.
155. McBride S, Sherman E, Tsai CJ, Baxi S, Aghalar J, Eng J, et al. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2021;39(1):30–7.
156. Pakkala S, Higgins K, Chen Z, Sica G, Steuer C, Zhang C, et al. Durvalumab and tremelimumab with or without stereotactic body radiation therapy in relapsed small cell lung cancer: a randomized phase II study. J Immunother Cancer. 2020;8(2):e001302.
157. Hu Y, Zhou M, Tang J, Li S, Liu H, Hu J, et al. Efficacy and Safety of Stereotactic Body Radiotherapy Combined with Camrelizumab and Apatinib in Patients with Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. Clin Cancer Res. 2023;29(20):4088–97.
158. Parikh AR, Szabolcs A, Allen JN, Clark JW, Wo JY, Raabe M, et al. Radiation therapy enhances immunotherapy response in microsatellite stable colorectal and pancreatic adenocarcinoma in a phase II trial. Nat Cancer. 2021;2(11):1124–35.
159. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin Radiat Oncol. 2008;18(4):240–3.
160. Ochoa-de-Olza M, Bourhis J, Coukos G, Herrera FG. Low-dose irradiation for reversing immunotherapy resistance: how to translate? J Immunother Cancer. 2022;10(7):e004939.
161. Zhang L, Li R, Chen H, Wei J, Qian H, Su S, et al. Human cytotoxic T-lymphocyte membrane-camouflaged nanoparticles combined with low-dose irradiation: a new approach to enhance drug targeting in gastric cancer. Int J Nanomedicine. 2017;12:2129–42.
162. Arnold SM, Regine WF, Ahmed MM, Valentino J, Spring P, Kudrimoti M, et al. Low-dose fractionated radiation as a chemopotentiator of neoadjuvant paclitaxel and carboplatin for locally advanced squamous cell carcinoma of the head and neck: results of a new treatment paradigm. Int J Radiat Oncol Biol Phys. 2004;58(5):1411–7.
163. Reiss KA, Herman JM, Zahurak M, Brade A, Dawson LA, Scardina A, et al. A Phase I study of veliparib (ABT-888) in combination with low-dose fractionated whole abdominal radiation therapy in patients with advanced solid malignancies and peritoneal carcinomatosis. Clin Cancer Res. 2015;21(1):68–76.
164. Wei J, Montalvo-Ortiz W, Yu L, Krasco A, Ebstein S, Cortez C, et al. Sequence of αPD-1 relative to local tumor irradiation determines the induction of abscopal antitumor immune responses. Sci Immunol. 2021;6(58):eabg0117.
165. Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. Int J Radiat Oncol Biol Phys. 2012;83(4):1306–10.
166. Scott JG, Berglund A, Schell MJ, Mihaylov I, Fulp WJ, Yue B, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. Lancet Oncol. 2017;18(2):202–11.
167. Monjazeb AM, Giobbie-Hurder A, Lako A, Thrash EM, Brennick RC, Kao KZ, et al. A Randomized Trial of Combined PD-L1 and CTLA-4 Inhibition with Targeted Low-Dose or Hypofractionated Radiation for Patients with Metastatic Colorectal Cancer. Clin Cancer Res. 2021;27(9):2470–80.
168. Schoenfeld JD, Giobbie-Hurder A, Ranasinghe S, Kao KZ, Lako A, Tsuji J, et al. Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol. 2022;23(2):279–91.
169. Welsh JW, Tang C, de Groot P, Naing A, Hess KR, Heymach JV, et al. Phase II Trial of Ipilimumab with Stereotactic Radiation Therapy for Metastatic Disease: Outcomes, Toxicities, and Low-Dose Radiation-Related Abscopal Responses. Cancer Immunol Res. 2019;7(12):1903–9.
170. Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, et al. Ipilimumab with Stereotactic Ablative Radiation Therapy: Phase I Results and Immunologic Correlates from Peripheral T Cells. Clin Cancer Res. 2017;23(6):1388–96.
171. Kroeze SGC, Pavic M, Stellamans K, Lievens Y, Becherini C, Scorsetti M, et al. Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium. Lancet Oncol. 2023;24(3):e121–e32.
172. Huang K, Prasad S, Ma SJ, Iovoli A, Farrugia M, Malik NK, et al. Long-term outcomes of single and five fraction schedules of stereotactic body radiation therapy for early-stage central or peripheral NSCLC: Neither fractionation nor location matter? Journal of Clinical Oncology. 2023;41(16_suppl):8538.
173. Arina A, Gutiontov SI, Weichselbaum RR. Radiotherapy and Immunotherapy for Cancer: From "Systemic" to "Multisite". Clin Cancer Res. 2020;26(12):2777–82.
174. Galluzzi L, Aryankalayil MJ, Coleman CN, Formenti SC. Emerging evidence for adapting radiotherapy to immunotherapy. Nat Rev Clin Oncol. 2023;20(8):543–57.
175. Koukourakis MI, Giatromanolaki A. Tumor draining lymph nodes, immune response, and radiotherapy: Towards a revisal of therapeutic principles. Biochim Biophys Acta Rev Cancer. 2022;1877(3):188704.

176. Venkatesulu B, Giridhar P, Pujari L, Chou B, Lee JH, Block AM, et al. Lymphocyte sparing normal tissue effects in the clinic (LymphoTEC): A systematic review of dose constraint considerations to mitigate radiation-related lymphopenia in the era of immunotherapy. Radiother Oncol. 2022;177:81–94.
177. Will immunotherapy really change radiotherapy? Lancet Oncol. 2019;20(12):1642–4.
178. Gensheimer MF, Gee H, Shirato H, Taguchi H, Snyder JM, Chin AL, et al. Individualized Stereotactic Ablative Radiotherapy for Lung Tumors: The iSABR Phase 2 Nonrandomized Controlled Trial. JAMA Oncol. 2023;9(11):1525–34.
179. Wang Y, Zhang T, Huang Y, Li W, Zhao J, Yang Y, et al. Real-World Safety and Efficacy of Consolidation Durvalumab After Chemoradiation Therapy for Stage III Non-small Cell Lung Cancer: A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2022;112(5):1154–64.
180. Tian S, Switchenko JM, Buchwald ZS, Patel PR, Shelton JW, Kahn SE, et al. Lung Stereotactic Body Radiation Therapy and Concurrent Immunotherapy: A Multicenter Safety and Toxicity Analysis. Int J Radiat Oncol Biol Phys. 2020;108(1):304–13.
181. Cortiula F, Reymen B, Peters S, Van Mol P, Wauters E, Vansteenkiste J, et al. Immunotherapy in unresectable stage III non-small-cell lung cancer: state of the art and novel therapeutic approaches. Ann Oncol. 2022;33(9):893–908.
182. Chen JL, Pan CK, Huang YS, Tsai CY, Wang CW, Lin YL, et al. Evaluation of antitumor immunity by a combination treatment of high-dose irradiation, anti-PDL1, and anti-angiogenic therapy in murine lung tumors. Cancer Immunol Immunother. 2021;70(2):391–404.
183. Hong S, Bi M, Yu H, Yan Z, Wang H. Radiation therapy enhanced therapeutic efficacy of anti-PD1 against gastric cancer. J Radiat Res. 2020;61(6):851–9.
184. Philippou Y, Sjoberg HT, Murphy E, Alyacoubi S, Jones KI, Gordon-Weeks AN, et al. Impacts of combining anti-PD-L1 immunotherapy and radiotherapy on the tumour immune microenvironment in a murine prostate cancer model. Br J Cancer. 2020;123(7):1089–100.
185. Grapin M, Richard C, Limagne E, Boidot R, Morgand V, Bertaut A, et al. Optimized fractionated radiotherapy with anti-PD-L1 and anti-TIGIT: a promising new combination. J Immunother Cancer. 2019;7(1):160.
186. Oweida A, Hararah MK, Phan A, Binder D, Bhatia S, Lennon S, et al. Resistance to Radiotherapy and PD-L1 Blockade Is Mediated by TIM-3 Upregulation and Regulatory T-Cell Infiltration. Clin Cancer Res. 2018;24(21):5368–80.
187. Rodriguez-Ruiz ME, Rodriguez I, Barbes B, Mayorga L, Sanchez-Paulete AR, Ponz-Sarvise M, et al. Brachytherapy attains abscopal effects when combined with immunostimulatory monoclonal antibodies. Brachytherapy. 2017;16(6):1246–51.
188. Young KH, Baird JR, Savage T, Cottam B, Friedman D, Bambina S, et al. Optimizing Timing of Immunotherapy Improves Control of Tumors by Hypofractionated Radiation Therapy. PLoS One. 2016;11(6):e0157164.
189. Hao Y, Yasmin-Karim S, Moreau M, Sinha N, Sajo E, Ngwa W. Enhancing radiotherapy for lung cancer using immunoadjuvants delivered in situ from new design radiotherapy biomaterials: a preclinical study. Phys Med Biol. 2016;61(24):N697–N707.
190. Habets TH, Oth T, Houben AW, Huijskens MJ, Senden-Gijsbers BL, Schnijderberg MC, et al. Fractionated Radiotherapy with 3×8 Gy Induces Systemic Anti-Tumour Responses and Abscopal Tumour Inhibition without Modulating the Humoral Anti-Tumour Response. PLoS One. 2016;11(7):e0159515.
191. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520(7547):373–7.
192. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res. 2009;15(17):5379–88.
193. Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin Cancer Res. 2005;11(2 Pt 1):728–34.
194. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys. 2004;58(3):862–70.
195. Chakravarty PK, Alfieri A, Thomas EK, Beri V, Tanaka KE, Vikram B, et al. Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer. Cancer Res. 1999;59(24):6028–32.

How to cite this article: Wu Y, Yi M, Niu M, Zhou B, Mei Q, Wu K. Beyond success: unveiling the hidden potential of radiotherapy and immunotherapy in solid tumors. Cancer Commun. 2024;44:739–760. https://doi.org/10.1002/cac2.12576