Review Article

Radiotherapy as salvage therapy and an adjunct to immunotherapy: exploring local and abscopal mechanisms to overcome immunotherapy resistance: a narrative review

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Background and Objective: Immune checkpoint inhibitors (ICIs) have ushered in a new era of therapies and play a significant role in the clinical treatment of a variety of tumors. However, immune resistance has increasingly created a bottleneck in treatment, making the question of how to overcome drug resistance an urgent issue to address. In this article, the mechanism of drug resistance is briefly described with a focus on how radiotherapy (RT) acts on the immune system to reverse immunotherapy failure. Combinations of existing treatment modalities need to be optimized to overcome resistance problems. Research has shown that some RT modalities reverse immune resistance or enhance efficacy when used in combination, which shows some value for immune resistance and is worthy of in-depth research.

Methods: In this review, we searched the literature published from 2000 to 2023 surrounding immunotherapy, RT and cancer.

Key Content and Findings: Based on the immune effects and immunosuppressive effects induced by RT, this review examined the preclinical rationales of RT and its clinical results. The findings indicate that RT might provide a novel regimen for patients with locally advanced tumors, especially oligometastatic tumors.

Conclusions: Salvage therapy with RT after immunotherapy resistance is the focus of current research. Other strategies, such as multidrug combination therapies, have made preliminary progress in preclinical experiments. Further research on the roles of different RT doses, fractionation regimens, and other treatment sequences in salvage therapy need to be conducted in the future. The optimal site and timing of low-dose radiotherapy are also undetermined, and prospective studies are need to determine the best regimen for optimizing patient treatment.

Keywords: Immunotherapy; resistance; radiotherapy (RT); salvage therapy; cancer

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Introduction

Cancer immunotherapy has made unprecedented progress over the past decade. The most widely used immunotherapeutic agents block antibodies against immunosuppressive receptors such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). However, a large number of antibodies and small molecules against other immune checkpoints [e.g., lymphocyte activation gene-3 (LAG3), T-cell immunoreceptor with Ig and ITIM domains, T cell immunoglobulin domain and mucin domain-3 (TIM3), B7 homolog 3 protein (B7H3), cluster of differentiation 39 (CD39), cluster of differentiation 73 (CD73), adenosine A2A receptor, and cluster of differentiation 47 (CD47) are also being gradually studied and applied in clinical practice (1). Despite the widespread use of immune checkpoint inhibitors (ICIs), only select patients benefit from immunotherapy, and multiple resistance mechanisms impair immune responses. Radiotherapy (RT) plays a key role in overcoming immune resistance. Thus, research needs to be conducted to understand the effects of RT on the immune system, and to explore which RT modes can improve the efficacy of treatments for patients who have received immune drugs. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-57/rc).

Methods

In this review, the PubMed database was searched to retrieve relevant articles using the following keywords: immunotherapy, RT, and cancer. We obtained relevant clinical trials from American Society of Clinical Oncology (ASCO) annual meeting abstracts and Clinicaltrials.gov. We also conducted manual searches of the reference lists of the retrieved articles, engaged in discussions with co-authors and experts in the field, and asked for details of the personal experiences of senior authors who had participated in and written expert reviews of the literature on similar topics to identify relevant articles. Both preclinical and clinical studies were evaluated (*Table 1*).

Resistance of immunotherapy

Immunotherapy is effective at multiple tumor sites, and unprecedented durable response rates have been observed; however, immunotherapy can often fail in patients due to tumor progression and resistance (2-4). Clinically, immunotherapy resistance mechanisms can be divided into the following three types (3): (I) primary resistance, which refers to a clinical scenario in which a cancer does not respond to an immunotherapy strategy; (II) adaptive immune resistance, which refers to a mechanism of resistance where a cancer is recognized by the immune system but it protects itself by adapting to the immune attack; and (III) acquired resistance, which defined as a clinical scenario in which cancer initially responds to immunotherapy but later relapses or progresses, irrespective of the time elapsed since the initial response (3). Current understandings of the effects of these mechanisms are described below.

Effects of tumor cell extrinsic factors

The tumor microenvironment (TME) plays a crucial role in the suppression of anti-tumor immunity. It consists of tumor blood vessels, immune cells, and the various chemokines and cytokines they produce, which together inhibit the immune response (5-7). The immune cells involved include T cells, antigen-presenting cells, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and natural killer (NK) cells (8-10). Among these, regulatory T cells (Tregs), MDSCs, and M2 macrophages are particularly involved in resistance to cancer therapies.

Preclinical studies have shown that removing Tregs from the TME can enhance anti-tumor immunity (11,12). MDSCs contribute to tumor invasion and metastasis, as well as decreased survival following cancer treatment (13-15). TAMs are divided into M1 and M2 phenotypes: M1 macrophages stimulate anti-cancer immunity by engulfing and killing tumor cells (16,17), while M2 macrophages promote tumor progression through secretion of growth and immunosuppressive factors like interleukin 10 (18,19). In addition, inhibitory cytokines like transforming growth factor beta (TGF-β) suppress immune responses by stimulating Tregs, and elevated TGF-β levels are associated with poor prognosis in many tumor types (20,21).

Chemokines such as C-C motif ligand 5 (CCL5), C-C motif ligand 7 (CCL7), and C-X-C motif ligand 8 (CXCL8) secreted by tumor cells recruit MDSCs and Tregs to the TME, where they contribute to immune suppression (22). C-C chemokine receptor type 4 (CCR4) helps to recruit Tregs, promoting their localization within the TME (23). Additionally, adenosine, produced by tumors, acts as an

Table 1 The search strategy summary

Items	Specification
Dates of search	11/01/2023 to 02/01/2024
Databases and other sources searched	PubMed.gov, ASCO annual meeting abstracts, Clinicaltrials.gov, manual searches of the reference lists of the retrieved articles
Search terms used	Immunotherapy, radiotherapy, and cancer
Timeframe	Studies published from 2000 to 2023
Inclusion and exclusion criteria	Inclusion criteria: (I) original research, reviews, meta-analysis; (II) peer reviewed English literature; (III) articles focusing on immunotherapy and radiotherapy. Exclusion criteria: (I) non-English language publications; (IV) studies published before 2000
Selection process	Studies were initially screened by Y.Y., and an agreement was then reached among all the authors as to the literature, meeting abstracts, and online references to be used

ASCO, American Society of Clinical Oncology.

immunosuppressive molecule that aids tumor growth (24). The rapid proliferation of tumor cells and abnormal blood vessel formation create a hypoxic environment within the TME (25). Hypoxia promotes tumor metastasis and resistance to chemotherapy and radiation, as well as a poor prognosis for patients (26). Through the hypoxia-inducible factor 1-α (HIF-1α) pathway, hypoxia up-regulates pro-angiogenic factors like VEGF and the multidrug resistance gene, which increases tumor invasiveness and immune evasion (27,28). Hypoxia also maintains high levels of programmed cell death ligand 1 (PD-L1), contributing to resistance to ICIs, making tumor elimination more difficult (29-30).

Effects of tumor cell intrinsic factors

Major histocompatibility complexes (MHCs) are crucial for antigen recognition in anti-tumor immunity, with beta 2-microglobulin (B2M) stabilizing MHC class I molecules on the cell surface. Mutations in B2M can lead to the loss of MHC class I expression, impairing antigen presentation and allowing tumor cells to evade immune detection (31,32). Additionally, interferon-γ (IFN-γ) released by effector T cells enhances MHC class I and PD-L1 expression via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Mutations in JAK1 and JAK2, such as those seen in metastatic melanoma patients, have been linked to resistance to ICIs after initial responses to pembrolizumab (4,33).

The protein tyrosine phosphatase non-receptor type 2 (PTPN2) negatively regulates JAK1 and JAK2, promoting resistance to ICIs by mediating IFN-γ resistance. Studies have shown that knocking down PTPN2 can lead to tumor regression in mice, and combining PTPN2 knockdown with PD-1 blockade resulted in significant tumor elimination in treatment-resistant melanoma models (34,35).

Phosphatase and tensin homolog (PTEN) is a tumor suppressor that regulates the phosphoinositide 3-kinase/protein kinase b/mechanistic target of rapamycin (PI3K/AKT/mTOR) pathway. Loss of PTEN increases immunosuppressive cytokines and reduces T-cell effector functions, such as IFN-γ production. PTEN deletions, observed in some metastatic cancers like uterine leiomyosarcoma, contribute to resistance by bypassing PI3K pathway inhibition. Targeting this pathway with inhibitors such as wortmannin, MK-2206, or rapamycin has shown promise in reducing PD-L1 expression in PTEN-mutant cancers (36,37).

The WNT-β-catenin pathway impedes T-cell infiltration in tumors, and dysregulation of this pathway is associated with resistance to PD-1 therapies in melanoma and gastric cancer. In one study, a melanoma patient who initially responded to anti-PD-1 therapy developed metastases with a new increase in β-catenin expression and the disappearance of T-cell infiltration (38,39). WNT-β-catenin signaling was also shown to be dysregulated in more than half of gastric cancer patients (40-42). Furthermore, this pathway controls ferroptosis, an iron-dependent form of regulated cell death, which has been linked to cancer resistance (43-45). Ferroptosis is regulated by glutathione peroxidase 4 (GPX4), which protects Tregs from ferroptosis, and its inhibition can reverse immune resistance by inducing ferroptosis in Tregs (46,47). Studies suggest that targeting GPX4 with inhibitors like ML210, which covalently inhibit GPX4 and

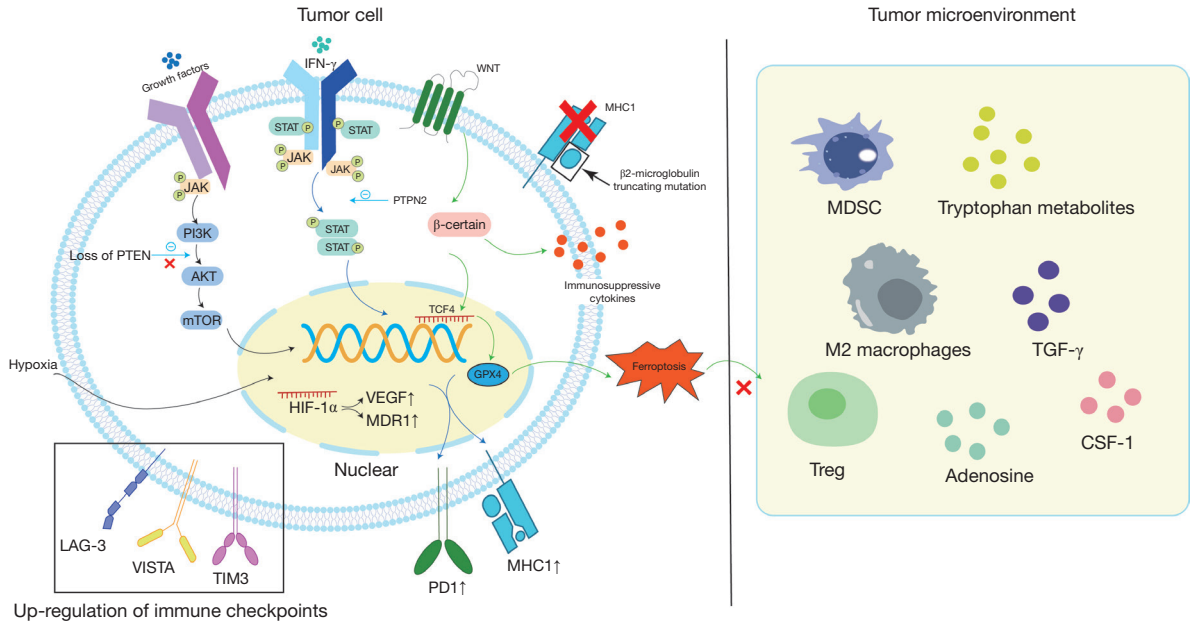

Figure 1 Mechanisms of resistance emerging from immunotherapy. Loss of the tumor suppressor gene PTEN activates the PI3K pathway The JAK-STAT pathway itself increases PD-1 and MHC class I expression, while PTPN2 decreases antigen presentation by inhibiting this pathway. The WNT pathway leads to drug resistance and increases tumor invasion. Truncating mutations in B2M lead to the loss of cell-surface expression of MHC class I, and the up-regulation of other immune checkpoints also contributes to resistance. β-certain protein can also inhibit ferroptosis through GPX4, which in turn allows increased Treg expression to suppress immunity. Immune cells and cytokines in the TME are immunosuppressive molecules. AKT, protein kinase B; B2M, beta 2-microglobulin; CSF-1, colony stimulating factor 1; GPX4, glutathione peroxidase 4; HIF-1α, hypoxia-inducible factor 1-α; JAK, Janus kinase; LAG3, lymphocyte activation gene-3; MDR, multidrug resistance; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; mTOR, mechanistic target of rapamycin; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; PTPN2, protein tyrosine phosphatase non-receptor type 2; STAT, signal transducer and activator of transcription; TCF4, T-cell factor 4; TGF-γ, transforming growth factor beta; TIM3, T cell immunoglobulin domain and mucin domain-3; TME, tumor microenvironment; VEGF, vascular endothelial growth factor; VISTA, v-domain Ig suppressor of T cell activation.

induce ferroptosis, may reverse immune resistance (48). Abnormal lipid metabolism in tumors also contributes to resistance to ICIs. Tumor-infiltrating lymphocytes (TILs) accumulate cholesterol upon entering the TME, leading to the upregulation of co-inhibitory molecules such as PD-1, lymphocyte activation gene-3 (LAG-3), and T cell immunoglobulin domain and mucin domain-3 (TIM-3), which contribute to a dysfunctional T-cell phenotype (49,50). Some studies have shown that reducing lipid production, such as with avasimibe which inhibits acetyl-CoA acyltransferase 1 (ACAT1), enhances $CD8^+$ T-cell function and can reverse resistance to ICIs in preclinical models (51-53) (*Figure 1*).

Effects of RT on tumor cells

RT kills both cancerous and normal cells by causing irreparable DNA damage, although its primary therapeutic effect is targeted at tumor cells. This damage includes multiple single-strand DNA breaks that eventually lead to double-strand breaks, which cannot be repaired by the cell's intrinsic DNA repair mechanisms. As a result, tumor cells undergo necrosis and apoptosis, releasing tumor-associated antigens in the process (54,55). RT also damages the tumor's microenvironment, including cell membranes, DNA, and endothelial cells, contributing to tumor cell death (56,57).

The immune system detects these antigens, with MHC class I molecules playing a key role in presenting tumor antigens on antigen-presenting cells, triggering $CD8^+$ T cells to recognize and destroy the tumor cells (58). However, tumor cells can downregulate MHC class I expression, enabling them to evade immune detection (59). An animal study demonstrated that MHC class I expression

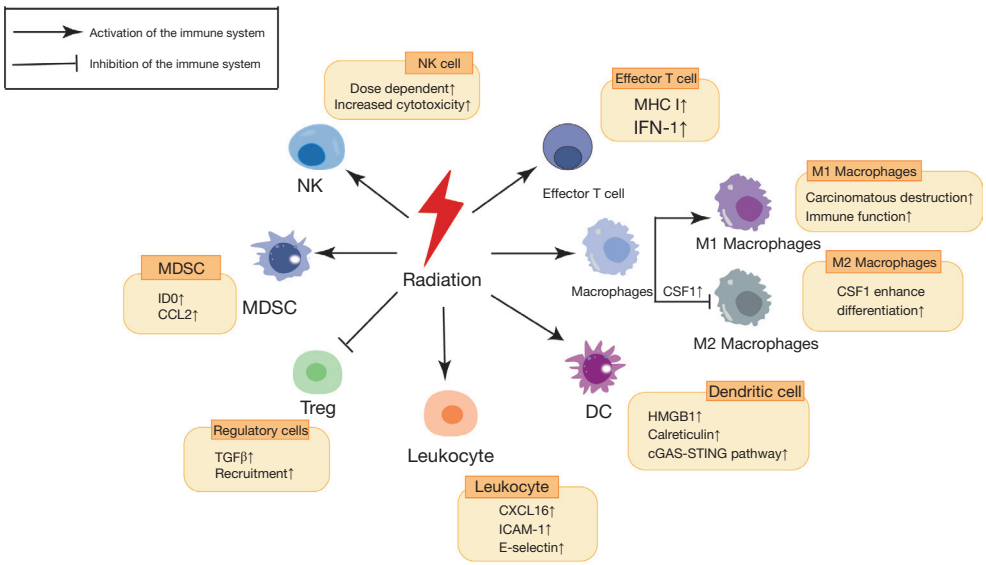

Figure 2 Effect of RT on immune cells in the TME. RT increases the number of immune cells by stimulating the expression of corresponding molecules and pathways, and different immune cells have different effects on the TME. The functions of the associated immune cells are indicated by arrows (solid arrows: activating immune system; vertical-horizontal lines: suppressing immune system). The upper arrow in the box indicates that RT increases its expression level. CCL2, C motif chemokine ligand 2; CSF1, colony stimulating factor 1; CXCL16, C-X-C motif chemokine ligand 16; ICAM1, intercellular adhesion molecule 1; IFN, interferon; IDO, indoleamine 2,3-dioxygenase; MDSC, bone marrow-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer; RT, radiotherapy; TGF-β, transforming growth factor beta; TME, tumor microenvironment; DC, dendritic cell.

increased in a dose-dependent manner after radiation (25 Gy) in mouse kidneys, with radiation-induced activation of mechanistic target of rapamycin (mTOR) enhancing MHC class I presentation (60).

Radiation-induced DNA damage can also lead to the release of neoantigens, which enhance the immune system's ability to recognize the tumor. In preclinical models, RT significantly increased the release of high mobility group box 1 (HMGB1) and promoted the translocation of calreticulin to the cell surface. This "eat me" signal activates dendritic cells (DCs), which are crucial for initiating the immune response. Furthermore, radiation increases the release of HMGB1, which binds to toll-like receptor 4 (TLR4) receptors on DCs, promoting their activation and enhancing the anti-tumor immune response (61-64).

RT: a double-edged sword in the immune system

RT is involved in the regulation of many immune processes, including the release and presentation of antigens, the priming and activation of T lymphocytes, the recruitment and accumulation of T cells in tumors, and the recognition of T lymphocytes (65) (*Figure 2*). RT can normalize the tumor vasculature and induce T-cell homing and penetration into the TME (66,67). The effects of RT on the immune system are multifaceted, necessitating an examination of its mechanisms of action from both advantageous and detrimental perspectives.

RT promotes the anti-tumor immune response

RT has the potential to enhance the recruitment and maturation of DCs, thereby facilitating the development of T-cell immunity. DCs, which are known for their exceptional ability to present antigens, play a crucial role in initiating adaptive immune responses following antigen uptake. The underlying mechanism of this effect may involve the induction of immunoglobulin M binding to complement anaphylatoxins released because of complement activation triggered by necrotic tumor cells (68,69).

In the case of RT, the activation of DCs may be driven by HMGB1 or calreticulin, or both. Stimulator of interferon genes (STINGs) are critical mediators of DC activation. STING pathway activation occurs when cyclic guanosine

monophosphate (GMP)-adenosine monophosphate (AMP) synthase detects DNA from tumor cells taken up by antigen-presenting cells (APC) (70). STINGs recruit and phosphorylate tank-binding kinase 1 in the nucleus, which activates interferon regulatory factor 3 (IRF3), and IRF3 induces the expression of type I interferon (71). Typically, a robust immune system serves as a safeguard against aberrations in the body; however, the emergence of tumors poses a challenge to immune cell infiltration (72).

Radiation enhances lymphocyte infiltration through two major mechanisms: changes in the vascular endothelium, and increased chemokine inducer expression. Research has shown that radiation increases the expression of E-selectin and Intercellular adhesion molecule 1 (ICAM-1) in human endothelial cells, which belong to cell adhesion molecules on the luminal surface of the endothelium, contributing to leukocyte extravasation (73). In addition, the expression and soluble release of the radiation-induced chemokine C-X-C motif chemokine ligand 16 (CXCL16) were observed in an induced mouse and human breast cancer cell line study. CD8 T cells expressing the CXCL16 receptor CXCR6 CD8 T cells, which express the CXCL16 receptor CXCR6, can be recruited to the site of inflammation or tumors (74).

Immunosuppression: an inevitable double-edged sword

Despite the beneficial effects of RT on the immune system, it also has the capability to induce the recruitment of MDSCs, primarily through the interaction with the monocyte chemoattractant C-C motif chemokine ligand 2 (CCL2). A study has shown that indoleamine 2,3-dioxygenase (IDO) expression after RT is associated with increased MDSCs, which is considered a major coordinator of immunosuppression in the TME (75). Considering the aforementioned mechanisms that contribute to immunosuppression, the inhibition of IDO presents a potential avenue for enhancing the therapeutic efficacy of RT and mitigating the immunosuppressive elements in the TME (76,77). The knockdown of CCL2 in a mouse colon tumor model resulted in complete tumor elimination in 60% of irradiated mice (78). Anti-CCL2 antibody treatment combined with RT also resulted in an increase in $CD8^+$ T cell activity; thus, RT-induced T-cell anti-tumor activity could be enhanced by blocking CCL2 (78). MDSC-targeted therapy combined with RT can also increase type I interferon production, and the recruitment of $CD8^+$ T cells (79,80). Radiation may increase Treg penetration into the TME by increasing TGF-β secretion (81-83), and radiation can dose-dependently increase the expression of $CD4^+CD25^+Foxp3^+$ Tregs, but it has an immunosuppressive function and is considered to be most associated with tumor escape (84). Combined treatment with RT and the CD25 antibody resulted in tumor growth reduction and transient regression in mice (82). RT may lead to a significant increase in the immunosuppressive cytokine TGF-β, but it down-regulates $CD8^+$ T cell proliferation and function and allows $CD4^+$ T cells to adopt a regulatory phenotype, thereby inhibiting the immune environment induced by RT (59).

In addition, TGF-β can protect cancer cells from DNA damage, thereby reducing the efficacy of RT (85). A study on breast cancer showed that the inhibition of TGF-β increased the radiosensitivity of breast cancer cells and promoted radiation-induced tumor growth delay (86). Epithelial cells from TGF-β-null mice and human cells in which TGF-β signaling was blocked pharmacologically were more sensitive to radiation as measured by the clonogenic survival of cells (87). Therefore, the inhibition of TGF-β before RT is effective in combination with fractionated RT (85).

Simultaneous irradiation triggered the polarization of M2-like cells toward TAMs with M1-like inducible nitric oxide synthase (iNOS) expression (66). Colony stimulating factor 1 (CSF1) is one of the main cytokines by which cancer cells regulate TAMs to exert an immunosuppressive function (88). CSF1 facilitates the recruitment of monocyte-derived macrophages to the tumor bed and differentiates them into an M2-like phenotype (89). RT can be combined with colony-stimulating factor 1 receptor (CSF1R) inhibitors to achieve better anti-tumor effects. A clinical study of patients with cervical cancer showed increased cytotoxic activity of circulating NK cells after RT of the primary tumor, which suggests that NK cells are activated by RT (90).

Immunotherapy resistance remains a critical challenge in cancer treatment, and understanding how to overcome it is essential for improving patient outcomes. RT has shown potential in modulating the immune response and enhancing the efficacy of immunotherapy. By adjusting the TME and influencing immune cell function, RT could play a crucial role in reversing immunotherapy resistance. Numerous studies have explored different modes of RT, and the impact of these approaches on overcoming resistance will be discussed in the following sections.

Hypofractionated RT in reversing immune resistance

Hypofractionated RT has been defined as a dose higher than 2.5 Gy per fraction. In hypofractionated RT, the single dose is increased to reduce the number of irradiation sessions.

Immune mechanisms and preclinical studies

One of the mechanisms leading to tumor resistance is the lack of tumor cell-surface antigens. Irradiated tumor cells provide effective tumor immunogens to DCs. Many preclinical studies have shown that doses greater than 7 Gy increase local interferon production, thereby enhancing antigen presentation in tumor cells (60,91,92). In one study, a Flt3 ligand (Flt3L) treatment and a single dose of local primary tumor irradiation (60 Gy) were administered to Lewis lung carcinoma (3LL/D122) grown in C57BL/6J mice for 10 days. The systemic treatment of Flt3L combined with RT resulted in the regression of the primary tumor, the induction of tumor-specific T-cell immunity, the reduction of lung metastases, and improved the survival of the combined treatment group compared to that of the control or Flt3L alone groups (93). Previous research has shown that blocking CTLA-4 alone did not inhibit the growth of tumors with low immunogenicity in a mouse breast cancer 4T1 model; however, when combined with 12 Gy × 2 fraction-treatments, the mice lived significantly longer (mean: 49 days; P<0.0005) than the other groups (94). Another study administered radiation with 12 Gy per fraction to subcutaneous mammary tumors in 4T1 mice and injected anti-PD-1 on days 0, 4, 8, and 12, and found that radiation enhanced anti-tumor immunity by enhancing the function of CD8 and NK cells compared to controls (95). In addition, radiation at 10 Gy per fraction slowed tumor growth in an A20 cell line model of subcutaneous B-cell lymphoma and an EL4 cell line model of T-cell lymphoma by increasing CD8-mediated tumor control (95).

Abscopal effect-related clinical trials

The clinical studies outlined below have confirmed the efficacy and safety of RT. In one study, 100 metastatic non-small cell lung cancer (mNSCLC) patients were divided into a pembrolizumab only group, pembrolizumab plus stereotactic body radiotherapy (SBRT) group (50 Gy in 4 fractions, delivered in this fashion if feasible), and a pembrolizumab plus hypofractionation RT group (45 Gy in 15 fractions). The objective response rate (ORR) was 25% (regardless of salvage RT) in the pembrolizumab only group (P=0.99), 38% in the pembrolizumab plus SBRT group, and 10% in the pembrolizumab plus hypofractionation RT group. In the patients who received pembrolizumab alone, the ORR outside the radiation field was 33% for those who received salvage SBRT (if needed) and 17% for those who received traditional salvage RT. This suggests that RT can enhance the efficacy of immunotherapy, and SBRT is more effective than conventional RT, but might be biased towards seeing a benefit in smaller tumors that could receive SBRT (96).

PEMBRO-RT and MD Anderson Cancer Center (MDACC) trials included 148 patients with mNSCLC, of whom 76 received pembrolizumab and 72 received pembrolizumab plus RT. The RT group was further divided into two subgroups: 24 Gy in 3 fractions and 50 Gy in 4 fractions. The best absolute risk reduction (ARR) was 19.7% in the pembrolizumab group, and 41.7% in the pembrolizumab plus radiation group [odds ratio: 2.96, 95% confidence interval (CI): 1.42–6.20; P=0.0039]. Median progression-free survival (PFS) was 4.4 months (interquartile range, 2.9–5.9 months) in the pembrolizumab alone group, and 9.0 months (interquartile range, 6.8–11.2 months) in the pembrolizumab plus radiation group (hazard ratio: 0.67, 95% CI: 0.45–0.99; P=0.045). The addition of radiation to pembrolizumab immunotherapy significantly increased the response rate of non-irradiated lesions, thereby significantly improving PFS and overall survival, but the study did not meet the predefined criteria for a meaningful clinical benefit. Therefore, larger sample size studies need to be conducted to more accurately examine the effects of immunotherapy plus RT on patient outcomes (97). A phase II trial (ChiCTR1900026175), known as the PRaG regimen, was conducted in patients with metastatic solid tumors to evaluate the efficacy of a combination of radiation, PD-1 inhibitors, and granulocyte-macrophage colony-stimulating factor (GM-CSF). The PRaG treatment cycle involved delivering three doses of 5 or 8 Gy to a metastatic lesion starting on day 1, followed by daily subcutaneous administration of 200 mg GM-CSF for 2 weeks, and then the administration of a PD-1 inhibitor intravenously within one week after completing RT. Notably, a patient with NSCLC, who had previously undergone single-agent PD-1 blockade therapy and achieved complete response (CR), demonstrated that combining radiation with GM-CSF can enhance immune

efficacy (98).

A phase-II clinical trial of ICE-PAC was conducted with metastatic castration-resistant prostate cancer (mCRPC) patients to improve treatment efficacy by combining RT and ICIs, as ICIs alone produced modest effects. The patients were treated with Avelumab (10 mg/kg) intravenously every 2 weeks for 24 weeks (12 cycles). A single fraction of stereotactic ablative radiotherapy (SABR) (20 Gy) was administered to one or two metastatic sites within 5 days before the first and second avelumab treatments. The study reported a disease control rate (DCR) of 48%, which met the prespecified primary endpoint. The ORR was 31%, and the median PFS was 8.4 months. Nearly half of the patients achieved durable disease control, about one-third had objective responses in both irradiated and non-irradiated lesions, and the toxicity of the combination was also acceptable; thus, adalimumab combined with SABR is promising in the treatment of refractory mCRPC (99).

In eight patients with metastatic/recurrent nasopharyngeal carcinoma, the confirmed ORR and DCR after three cycles of PD-1 monotherapy were 12.5% and 37.5%, respectively. Notably, the development of new distant metastatic lesions after 18 months occurred in a single patient who had initially achieved complete remission. Seven of these patients subsequently received SBRT (25–36 Gy/5–6 fractions, preferred six-part regimen, usually 5 Gy × 6), and the ORR of these seven patients was 85.7%, including 2 CRs (28.6%) and 4 partial responses (57.1%) These results suggest that RT can effectively reverse PD-1 inhibitor resistance. Among the seven patients who were resistant to PD-1 inhibitors, 85.7% had an ORR after receiving RT, and the median PFS and 2-year OS were 8 months and 71.0%, respectively (100).

In studies of metastatic prostate cancer, no difference in OS was found between the single-site radiation plus ipilimumab treatment group and the single-site radiation group, but benefits were observed in patients with small tumor burdens (101). Three doses of radiation of 8 Gy each combined with anti-CTLA-4 treatment were more effective than a single high dose of 20 Gy in controlling distal non-irradiated tumors in two-sided TSA breast cancer and MCA38 colon cancer models (102). A metastatic melanoma patient who showed disease progression on ipilimumab received palliative treatment of a paraspinal mass (9.5 Gy × 3 fractions) with SBRT and showed a 30-fold increase in antibody titers against the common melanoma tumor antigen NY-ESO-1 after RT compared to before (103). In another study, 16 patients with mCRPC were treated with ipilimumab monotherapy, and another 34 received ipilimumab plus 8 Gy per fraction of radiation. The results revealed a prostate specific antigen decrease of ≥50% in eight patients, a CR in one patient, and stable disease in six patients in the combination therapy group, which indicated that the addition of radiation increased the efficacy of immunotherapy (104).

Low-dose radiotherapy (LDRT) in reversing immune resistance

Immune mechanisms and preclinical studies

In a study of mice with pancreatic cancer, local LDRT (i.e., up to 2 Gy per fraction) was found to promote tumor infiltration by T cells through direct radiation effects on tumor tissue (66). Administering LDRT after antigen stimulation increases the number of B and T cells (105). The effect of LDRT on immune cell changes in the TME is shown in *Figure 3*.

Notably, LDRT was shown to increase antibody secretion and enhance antibody-dependent cytotoxic responses in tumor-bearing mice, both of which are strongly associated with tumor regression (106). Preclinical studies of xenograft mouse models have shown that radiation doses of up to 10–12 Gy per fraction may cause severe damage to the TME without damaging peripheral blood vessels, which is essential to adequately recruit CD8 lymphocytes to the tumor area in response to release of damage-associated molecular patterns (107-109). The pro-inflammatory response is detrimental to anti-tumor immunity, and LDRT can suppress this response (110).

Unlike high-dose radiation (HDR), which leads to fibrosis and increased TGF-β secretion and thus recruitment of Tregs into tumors (82), the delivery of 0.5 Gy × 4 LDRT to primary tumors following a single HDR helped to slow tumor growth, reduce Tregs, and suppress lung metastasis, as demonstrated in a 3LL mouse lung cancer model and 4T1 breast cancer model (111).

There may be time-sensitive effects when ICIs are combined with RT, especially LDRT, resulting in transient immune effects. Following the application of a single 1 Gy dose to an ID8 ovarian cancer mouse model, the RT-induced T-cell response in the tumor disappeared within a week but repeated 1 Gy irradiation was required to maintain immune infiltration. This may be associated with NKG2D-dependent interactions and RAE1-expressing DC subsets (112). LDRT led to increased iNOS expression

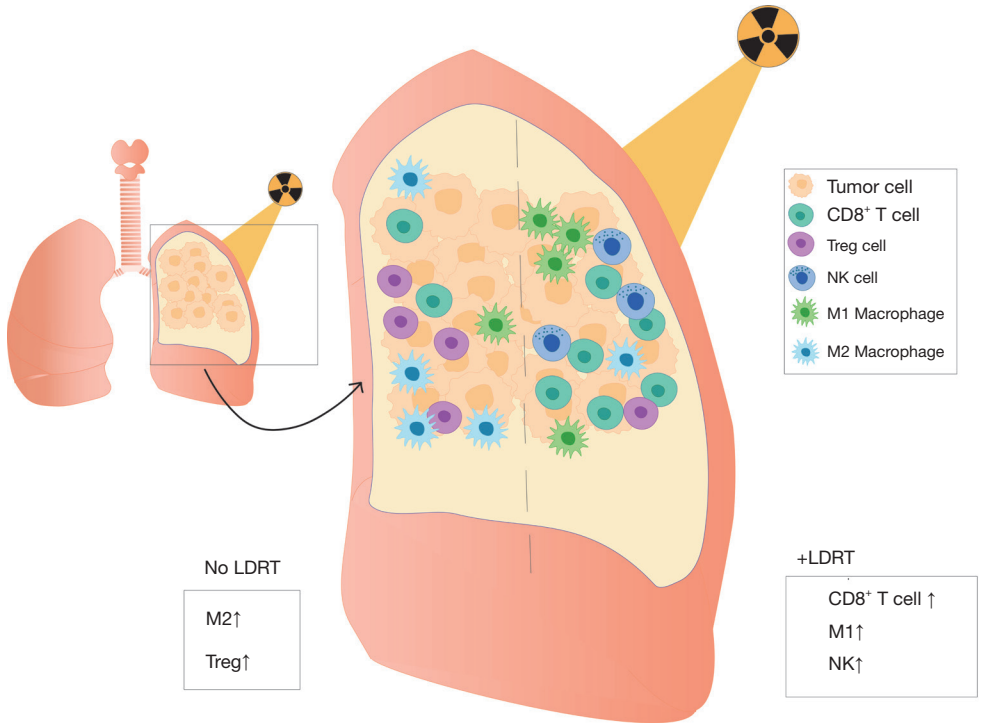

Figure 3 Immune cell changes in the TME after LDRT and no LDRT. M1, CD8, and NK cell migration increased after LDRT treatment, while M2 and Treg migration increased without RT. NK, natural killer; LDRT, low dose radiotherapy; TME, tumor microenvironment; RT, radiotherapy.

in macrophages from tumor-bearing RT5 mice receiving 2 Gy total body irradiation. Following the inhibition of iNOS, T cells, $CD11b^+$, and $CD68^+$ macrophages could not be recruited to the tumor, and the continued tumor progression suggests that iNOS has a promoting effect on immunity. Chronic low-dose rate irradiation stimulates innate immunity by enhancing the cytotoxicity of NK cells (113,114). Radiation increased the NK cell killing rates in 3LL Lewis lung carcinoma, and MCA105 and K562 cells, and the effect of RT on NK cells was dose-dependent (115). Additionally, preclinical studies of mice have demonstrated the stimulatory effects of LDRT on the proliferation of bone marrow hematopoietic progenitor cells (116,117). LDRT was shown to promote cutaneous wound healing by stimulating the peripheral mobilization of bone marrow stem cells in a diabetic rat model (118). LDRT exposed to 75 mGy at one time or 25 mGy at three times stimulated the expression and activity of superoxide dismutase in the kidney (119). These results indicate that LDRT can increase the levels of various antioxidants *in vitro* and *in vivo*, and then kill tumor cells by necrosis or apoptosis (120). In preclinical studies, a single RT dose of less than 2 Gy is considered LDRT. LDRT cannot directly kill tumor cells, but mainly acts by activating and stimulating immune cells, and promoting the transformation of tumor stroma into a more favorable microenvironment, thereby promoting the effects of immunotherapy (66).

Clinical trials

In an ongoing phase II clinical trial, one patient with metastatic melanoma of the liver, lung, bone, and brain continued to progress 1 month after receiving ipilimumab in combination with nivolumab. He was then treated with 5.6 Gy in 4 fractions to nearly the entire liver, and after 4 months of treatment, the patient showed a partial response in the liver, and an 83% reduction in tumor burden. A patient with human papillomavirus (HPV)-negative oropharyngeal squamous cell carcinoma took pembrolizumab after relapse, and responded completely to the treatment, but two years later, developed continued progression in the cervical lymph nodes (maximum lesion short axes: 1.0 and 1.5 cm) and right lower lobe lung nodules (long axis: 1.1 cm). After 50 Gy in 4 fractions to lung lesions and 7 Gy × 5 fractions to cervical

lymph node treatments and continued pembrolizumab treatment, the patient achieved complete remission after three months of treatment (121). A 20-year-old woman with fibrolamellar hepatocellular carcinoma and lung metastases was administered ipilimumab and sequential SABR after developing metastatic lesions in the lung; a lesion in the left lower lung received low-dose scattered radiation (3 Gy total), a lesion in the right lower lung did not receive (43) a scattered dose; the tumor in the left lower lobe decreased after 6 months, while the tumor in the right lower lobe progressed significantly; these findings indicate the significance of LDRT in the treatment of clinical lesions (122).

Conventional fractionated RT in reversing immune resistance

In hypofractionated RT, a single dose is increased to reduce the number of exposures, irradiating target volumes with greater precision and intensity. However, this type of RT still has some limitations, such as aggravated damage to normal tissues and greater side effects. Thus, conventional RT is still widely used in clinical settings. The international single fraction standard for conventional RT pairs is 1.8–2 Gy. A 70-year-old male patient with Merkel carcinoma, who was initially treated with adjuvant RT to the right groin and systemic carboplatin/etoposide, developed metastatic disease, but was then converted to single-agent pembrolizumab, and showed a partial response of 10 months, until progressive disease involving the left groin and left external iliac lymph nodes developed. Progressive left inguinal/pelvic disease was treated with conventional fractionated intensity-modulated RT at a dose of 45 Gy delivered in 25 fractions. There was no evidence of disease on imaging 20 months after RT (123).

Study of combined RT in reversing immune resistance

In a preclinical study, 344 SQ lung adenocarcinoma tumors were established bilaterally in 129 Sv/Ev mice, and a dual RT "RadScopal" therapy was established in which HDR was used for the primary tumor (to release antigen and primitive T cells) and LDRT was used for the secondary tumor (to modulate stroma and allow the infiltration and expansion of effector T cells and NK cells). The RadScopal therapy (HDR plus LDRT) was combined with anti-PD-1 and anti-CTLA-4 immunotherapy, preceded by HDR (3 fractions each of 12 Gy fractions). This triple combination resulted in 90% survival during a 50-day observation period with LDRT (2 fractions of 1 Gy fractions) after 3 days, significantly controlling both the primary and secondary tumors (124). The clinical outcomes of RT for salvage following the failure of immunotherapy studies and case series are shown in *Table 2* (96-101,121-123).

Clinical trials and prospective studies of RT as an immune adjuvant

Given that many preclinical studies and clinical cases have investigated the reversal of immune resistance by RT, its clinical prospects are eagerly awaited and require the support of subsequent data. To date, 177 clinical trials have been registered for LDRT on the official website of clinical trials, and there are also a large number of trials for SBRT. This research is mainly focused on mNSCLC, head and neck cancer, metastatic melanoma, and prostate cancer. A phase-II trial (NCT03480334) is being conducted with 29 patients with Hodgkin lymphoma who relapsed after anti-PD1 therapy to investigate the distant effects of RT and nivolumab. Due to the presence of distant effects, RT can enhance the efficacy of ICIs and also reverse drug resistance. Similarly, in another trial (NCT03354962), SBRT is being administered to metastatic melanoma patients who had been treated with PD-1 + CTLA-4 inhibitors to mediate distant effects to enhance efficacy. In addition, 180 patients with metastatic head and neck squamous cell carcinoma were included in a phase-II trial (NCT03386357) to compare the different effects of pembrolizumab alone versus pembrolizumab combined with SBRT. Hypofractionated RT was used to enhance the systemic immune response to ICIs in 35 patients with mNSCLC (in NCT03035890) at the recommended dose of 8–15 Gy in three fractions. Most of the clinical trials included patients who had relapsed after the use of ICIs and adopted a two-arm trial design. The experimental group was treated with immune drugs combined with RT, while the control group received immune drugs alone. The difference between the two groups was compared to evaluate the role of RT in enhancing the treatment.

Conclusions

Given the increasing role of immunotherapy in current clinical care, and the increasing number of patients receiving immunotherapy, primary and secondary resistance to ICIs is emerging as a new problem in

Table 2 Clinical outcomes of radiotherapy for salvage following the failure of immunotherapy studies and case series

Author	Research type	Immunotherapy	Number	Tumor species	Radiotherapy mode	Dose (Gy)/fraction	OS, months	ORR, %
Patel *et al.*, 2021 (121)	Single-arm clinical trial	Pembrolizumab	1	Non-small cell lung cancer	LDRT	6 Gy/4 fractions	10	25
Patel *et al.*, 2021 (121)	Single-arm clinical trial	Ipilimumab, nivolumab	1	Non-small cell lung cancer	LDRT	5.6 Gy/4 fractions	6	42
Patel *et al.*, 2021 (121)	Single-arm clinical trial	Pembrolizumab	1	Non-small cell lung cancer	LDRT	7 Gy/5 fractions	12	15
Menon *et al.*, 2019 (122)	Single-arm clinical trial	Ipilimumab	1	Non-small cell lung cancer	LDRT	3 Gy total	6	–
Welsh *et al.*, 2020 (96)	Retrospective cohort study	Pembrolizumab	100	Non-small cell lung cancer	SBRT, conventional fractionated RT	50 Gy/4 fractions; 45 Gy/15 fractions	–	38
Kong *et al.*, 2022 (98)	Prospective single-arm study	PD-1 inhibitors	50	Non-small cell lung cancer	SBRT	5 Gy/3 fractions	9.6	13.2
Theelen *et al.*, 2021 (97)	Pooled analysis of two randomized trials	PD-1 inhibitors	148	Non-small cell lung cancer	SBRT	15 Gy/3 fractions	9	–
Kwan *et al.*, 2022 (99)	Prospective phase-II study	Avelumab, adalimumab	41	Prostate cancer	SBRT	30 Gy/4 fractions	–	31
Lin *et al.*, 2022 (100)	Retrospective single-arm study	PD-1 inhibitors	8	Metastatic cancer	SBRT	25–36 Gy/ 5–6 fractions	–	85.7
Bloom *et al.*, 2019 (123)	Single-arm clinical trial	Pembrolizumab	1	Merkel carcinoma	Conventional fractionated RT	27 Gy/9 fractions	20	–
Kwon *et al.*, 2014 (101)	Multicenter randomized double-blind controlled trial	Ipilimumab	399	Prostate cancer	SBRT	8 Gy/fraction	11.2	–

LDRT, low-dose radiotherapy; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; RT, radiotherapy; SBRT, stereotactic body radiotherapy.

daily clinical routine. Salvage therapy with RT after immunotherapy resistance is the focus of current research, and other strategies such as multidrug combination have made preliminary progress in preclinical experiments. Currently, clinical evidence regarding the optimization of RT parameters and their synergistic effects with immunotherapy remains heterogeneous, and there is no established consensus on the optimal RT parameters, which still require further exploration. Further research should be conducted on the role of different RT doses, fractionation regimens, RT and other treatment sequences in salvage therapy in the future. The optimal site and timing of LDRT are also undetermined, and clinical trials and prospective studies need to be conducted to determine the best regimen to optimize patient treatment.

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Footnote

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