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REVIEW

Dual Targeting of Inflammatory and Immune Checkpoint Pathways to Overcome Radiotherapy Resistance in Esophageal Squamous Cell Carcinoma

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Abstract: Esophageal squamous cell carcinoma (ESCC) is characterized by chronic inflammation, immune evasion, and resistance to RT. Inflammatory pathways such as nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3), and cyclooxygenase 2 (COX-2) promote tumor progression and reduce radiosensitivity. RT activates pro-inflammatory cytokines and upregulates immune checkpoints including programmed death 1 (PD-1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), which contribute to immune suppression and treatment failure. Dual targeting of inflammatory and immune checkpoint pathways has shown potential to reverse radio resistance and enhance therapeutic response. Inhibition of COX-2 can reduce inflammation and improve tumor control, while blockade of PD-1 can restore T cell function and promote antitumor immunity. Strategies that integrate anti-inflammatory components, immune checkpoint inhibitors (ICIs), and RT guided by molecular profiling may improve treatment outcomes in ESCC. This review focuses on the biological basis of inflammation-mediated radio resistance and presents dual targeting approaches as promising options to overcome current therapeutic limitations.

Keywords: esophageal squamous cell carcinoma, inflammation, radiotherapy (RT) resistance

Introduction

ESCC remains an aggressive malignancy with poor prognosis despite advances in early detection and multimodal treatments. Chronic inflammation, tumor microenvironment (TME), and resistance to RT contribute to its complexity, necessitating novel therapeutic strategies to improve patient outcomes.[1]

Inflammation is a key driver of ESCC progression, fueled by exposure to environmental carcinogens such as tobacco, alcohol, and dietary irritants. This results in oxidative stress, cytokine secretion, and immune cell infiltration, activating oncogenic pathways including NF-κB, STAT3, and COX-2/PGE2, which collectively promote tumor growth, immune evasion, and genomic instability.[2] The inflammatory milieu fosters an immunosuppressive TME, further contributing to therapy resistance.[3]

RT influences the immune milieu through context-dependent pro-inflammatory and anti-inflammatory mechanisms that shape therapeutic outcomes in ESCC.[4,5] Combining RT with immunotherapy offers a promising strategy to overcome resistance. RT induces ICD, enhancing antigen presentation and dendritic cell recruitment, thereby activating cytotoxic T cells.[6,7] However, RT also upregulates immune checkpoint molecules such as PD-1 and programmed death ligand 1

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(PD-L1), leading to T cell exhaustion and therapy resistance.[8] Integrating RT with ICIs has demonstrated synergistic effects, restored T cell function, and improved tumor control.[9] Targeting TME modulators such as transforming growth factor-beta (TGF-β) and VEGF further enhances RT response by counteracting immunosuppression and facilitating immune infiltration.[10]

Beyond ICIs, anti-inflammatory factors such as NSAIDs and COX-2 inhibitors are being explored as radiosensitizers in ESCC, as they attenuate RT-induced inflammation and suppress tumor-promoting pathways.[11,12] Additionally, metabolic adaptations within the TME contribute to radio resistance, with alterations in glucose and lipid metabolism supporting tumor survival. Inhibiting glycolysis, glutaminolysis, or lipid biosynthesis represents a potential strategy to improve RT efficacy.[13,14]

Advancements in biomarker-driven and AI-assisted RT planning offer further opportunities to optimize ESCC treatment.[15,16] Identifying predictive biomarkers, such as circulating inflammatory cytokines, immune cell profiles, and radio resistance signatures, will facilitate patient stratification and therapy selection.[17] Integrating RT with novel therapies targeting inflammation, the TME, and metabolic pathways has the potential to improve clinical outcomes.[18,19]

ESCC remains a challenging malignancy due to its aggressive progression and resistance mechanisms driven by inflammation and RT. While RT remains fundamental, its efficacy is often limited by inflammatory responses and an immunosuppressive TME. Emerging approaches, including RT-ICI combinations, TME-targeting therapies, and metabolic inhibitors, offer promising avenues for enhancing therapeutic responses. A deeper understanding of these intricate interactions will be essential for developing personalized treatment strategies that improve survival and quality of life for ESCC patients.[20–22] Inflammation-mediated radio resistance in ESCC is shaped by RT dose and fractionation. Hyperfractionation can reduce IL-6 and suppress pro-inflammatory signaling,[23,24] while stereotactic RT may increase TGF-β and other immunosuppressive mediators,[25] suggesting a dose-dependent inflammatory modulation relevant for treatment design. Stereotactic body radiation therapy (SBRT) has also been found to be associated with elevated TGF-β expression and an immunosuppressive TME.[26–28] In Asian ESCC populations, IL-1β polymorphisms associated with betel quid exposure have been linked to chronic inflammation and elevated cancer risk,[29] highlighting the need for population-adapted anti-inflammatory approaches. Concurrently, metabolic reprogramming in ESCC, including upregulation of fatty acid synthase (FASN), glucose transporter 1 (GLUT1), and sterol regulatory element-binding protein 1 (SREBP1), contributes to radio resistance and offers potential targets for radio sensitization.[22,30,31] These mechanistic insights align with recent Phase II clinical trials investigating RT combined with ICIs in ESCC, which show promising clinical activity.[32,33] These studies report improved response rates and progression-free survival, supporting the feasibility of dual targeting strategies.

Here, this review focuses on the ESCC-specific mechanisms by which inflammation drives radio resistance and highlights therapeutic strategies centered on dual targeting of inflammatory and immune checkpoint pathways as a promising approach to enhance RT efficacy and outcomes.

Inflammation in ESCC Development and Progression

Inflammation is a fundamental driver of ESCC initiation, progression, and resistance to therapy. Chronic inflammation, exacerbated by infections, environmental exposures, and dysregulated immune responses, establishes a tumor-promoting microenvironment that facilitates malignant transformation. Recent studies have provided deeper insights into the molecular mechanisms underlying inflammation in ESCC, highlighting novel therapeutic targets and biomarkers.

Inflammation as a Hallmark of Cancer

Chronic inflammation is a well-established hallmark of cancer, playing a critical role in ESCC pathogenesis. Persistent inflammatory stimuli induce DNA damage, genomic instability, and the activation of oncogenic pathways, collectively driving tumorigenesis. In ESCC, chronic inflammation is frequently triggered by infections, including human papillomavirus (HPV) and *Helicobacter pylori*, as well as environmental factors such as tobacco smoking, alcohol consumption, and dietary carcinogens.[34] These factors generate a pro-inflammatory microenvironment that facilitates the transformation of normal esophageal epithelial cells into malignant counterparts.

HPV infection has been linked to ESCC.[35] It has been demonstrated that HPV oncoproteins E6 and E7 disrupt key cellular regulatory mechanisms, notably the p53 and Rb pathways, leading to uncontrolled cell proliferation and immune evasion.[36,37] Similarly, *H. pylori*, historically associated with gastric cancer.[38] However, recent findings indicate HPV16E6 infection drives an inflammatory TME in ESCC by inducing M2 macrophage polarization, which enhances tumor invasion and metastasis through increased MMP-9 expression.[39]

Environmental carcinogens further exacerbate chronic inflammation and enhance ESCC progression.[40] Tobacco smoke generates oxidative stress and DNA damage, thereby activating key inflammatory signaling pathways such as NF-κB, which support tumor cell survival, proliferation, and angiogenesis.[41–45] Additionally, dietary carcinogens, including nitrosamines found in preserved foods, contribute to the inflammatory microenvironment that fosters ESCC development.[46] These findings underscore the multifactorial nature of ESCC and the pivotal role of inflammation in its pathophysiology.

Key Inflammatory Pathways in ESCC

The NF-κB pathway is a critical regulator of inflammation and a major driver of ESCC progression. Activated by pro-inflammatory cytokines, infections, and environmental stressors, NF-κB orchestrates the transcription of genes that promote cell survival, proliferation, and immune evasion (Figure 1A).[47]

Recent study revealed that NF-κB is constitutively activated in ESCC, upregulating cytokines such as TNF-α, which further sustain chronic inflammation.[48] NF-κB also interacts with other oncogenic pathways, including STAT3 and COX-2, forming a pro-tumorigenic signaling network. The JAK/STAT3 pathway promotes ESCC progression by driving cancer-related inflammation through crosstalk with NF-κB and COX-2, highlighting STAT3 as a potential therapeutic target.[49] PAR1 promotes ESCC progression through FAK/PI3K/AKT/STAT3/NF-κB signaling, while PAR4 inhibits tumor growth via nSMase2/MAPK/NF-κB, highlighting NF-κB and STAT3 as key regulators in ESCC pathogenesis.[50]

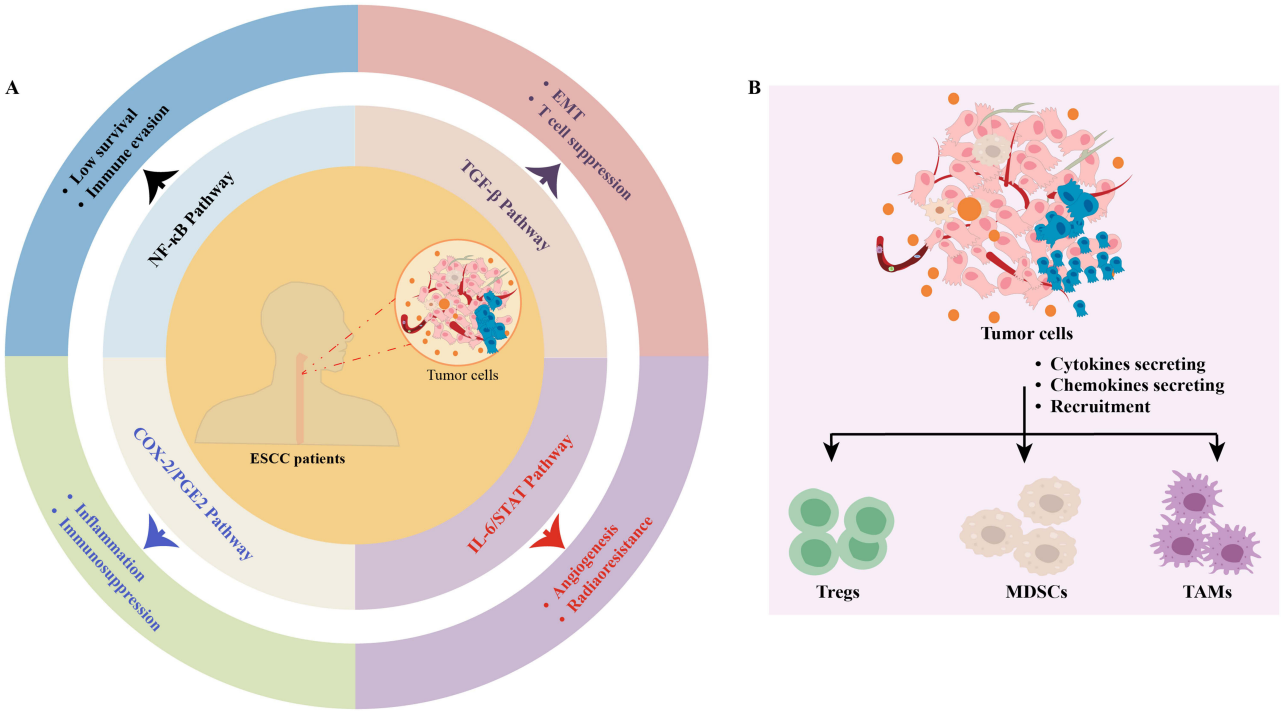

Figure 1 Key Inflammatory Pathways in ESCC. (**A**) Schematic illustration of key inflammation-related signaling pathways contributing to ESCC progression. Chronic inflammatory stimuli activate pathways such as NF-κB, IL-6/STAT3, COX-2/PGE2, and TGF-β, which promote tumor survival, immune evasion, angiogenesis, EMT, and resistance to therapy. These interconnected pathways establish a tumor-promoting and immunosuppressive microenvironment in ESCC; (**B**) Tumor cells secrete cytokines and chemokines that recruit TAMs, Tregs, and MDSCs, collectively enhancing tumor growth and facilitating immune evasion.

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The STAT3 pathway is another key regulator of inflammation in ESCC, linking chronic inflammatory signals to tumor progression and immune suppression (Figure 1A). MEK inhibition in ESCC induces STAT3 activation through SOCS3 downregulation, linking inflammation to tumor progression and therapy resistance.[51] High STAT3β expression in ESCC enhances sensitivity to platinum-based chemoradiotherapy (CRT) by upregulating the TNF signaling and necrotic cell death pathways, linking STAT3-mediated inflammation to treatment response.[52] TGFβ-induced LAMC1 upregulation in ESCC activates Akt–NF-κB–MMP9/14 signaling to promote tumor progression while enhancing CXCL1 secretion, which drives inflammatory cancer-associated fibroblast (CAF) formation through CXCR2–pSTAT3 signaling.[53] Additionally, extracellular vesicle-loaded IL-32 from ESCC cells is internalized by macrophages, inducing M2 polarization through the FAK-STAT3 pathway and promoting an inflammatory TME that drives metastasis.[54] Given its pivotal role in linking chronic inflammation to tumor progression and therapeutic resistance, STAT3 represents a critical target for disrupting inflammatory pathways that sustain ESCC malignancy.

The COX-2/PGE2 pathway is another significant contributor to inflammation-driven carcinogenesis in ESCC (Figure 1A). COX-2 is frequently overexpressed in ESCC tissues and correlates with poor prognosis. PGE2, through its EP2 receptor, transactivates EGFR in ESCC cells, promoting inflammation-driven tumor progression by enhancing cell proliferation, invasion, and the secretion of pro-inflammatory cytokines via the COX-2/PGE2 axis.[55] Negative COX-2 expression in ESCC is linked to reduced tumor-associated inflammation, enhanced radiosensitivity, and improved treatment response, underscoring the role of the COX-2/PGE2 axis in modulating inflammation-driven resistance to RT.[56] Moreover, AHR promotes ESCC progression by activating the COX-2/PGE2/STAT3 axis, and its inhibition via genetic knockdown or DIM treatment suppresses tumor growth, migration, and inflammation-driven tumor progression.[57]

Cytokines such as IL-6 and IL-10 further reinforce the inflammatory microenvironment in ESCC. IL-6 promotes ESCC progression and inflammation through EGFR signaling, where MSA-mediated upregulation of miR-146a suppresses EGFR expression, subsequently reducing IL-6 secretion and disrupting the inflammatory TME in an IL-6-dependent manner.[58] IL-6 also promotes ESCC progression and inflammation by activating STAT3 signaling (Figure 1A), which upregulates NANOG expression, thereby enhancing cancer cell proliferation, invasion, and stemness through the induction of downstream oncogenic targets.[59] Likewise, IL-10 promotes inflammation and immune evasion in ESCC by upregulating PD-L1 and Met signaling, creating an immunosuppressive TME that enhances tumor progression, while targeting IL-10 in combination with PD-L1 blockade may offer a potential therapeutic strategy.[60] In addition, IL-10 contributes to immune evasion in ESCC by interacting with the INPP5A/HLA-G1/MMP-21 regulatory network, promoting an immunosuppressive microenvironment that facilitates tumor progression and inflammation-mediated carcinogenesis.[61]

The dynamic interaction between immune cells and cancer cells within the ESCC microenvironment significantly influences tumor progression. Tumor cells have been shown to secrete cytokines and chemokines that recruit immunosuppressive immune cells, including TAMs, Tregs, and MDSCs (Figure 1B), collectively enhancing tumor growth and facilitating immune evasion.[62] For instance, TAMs produce IL-10 and TGF-β, suppressing cytotoxic T cell activity and enhancing angiogenesis.[63] Similarly, TAMs drive ESCC progression by secreting the chemokine CCL22, which activates CCR4-mediated FAK/AKT signaling, fostering an inflammatory TME that promotes malignancy and therapy resistance.[64] Those pathways (Table 1) orchestrate inflammation-driven ESCC progression by promoting tumor proliferation, immune suppression, metastasis, and therapy resistance, making them critical targets for disrupting inflammation-mediated carcinogenesis. The major inflammation-related pathways involved in ESCC progression and radio resistance are illustrated in Figure 1.

Inflammatory Biomarkers in ESCC

C-reactive protein (CRP) is a systemic inflammatory biomarker that has been correlated with poor prognosis in ESCC patients. Elevated CRP levels have been significantly correlated with advanced tumor stage, lymph node metastasis, and reduced overall survival in ESCC.[65] CRP production is driven by IL-6, further emphasizing the impact of systemic inflammation on ESCC progression.[66] IL-6 and IL8 not only activates oncogenic pathways such as STAT3 but also drives systemic inflammation and immune suppression, promoting tumor aggressiveness and metastasis.[67,68] The neutrophil-to-lymphocyte ratio (NLR) serves as an indicator of immune dysregulation, predicting poor prognosis and resistance to

Table 1 Key Inflammatory Pathways in ESCC

Pathway	Mechanism in ESCC	Therapeutic Implications	References
NF-κB	Activated by pro-inflammatory cytokines, infections, and stressors, NF-κB promotes cell survival, proliferation, and immune evasion. NF-κB interacts with STAT3 and COX-2, sustaining chronic inflammation and tumor progression.	Targeting NF-κB signaling may disrupt chronic inflammation and tumor-promoting networks, potentially improving treatment outcomes.	[47–50]
STAT3	STAT3 links chronic inflammation to tumor progression and immune suppression. MEK inhibition leads to STAT3 activation via SOCS3 downregulation, promoting therapy resistance. STAT3 also enhances tumor progression via TNF signaling and inflammatory CAF formation.	Inhibiting STAT3 can reduce inflammation-driven malignancy and enhance CRT response.	[51–54]
COX-2/PGE2	COX-2 is overexpressed in ESCC and promotes tumor progression by activating PGE2-EP2-EGFR signaling, leading to increased proliferation, invasion, and cytokine secretion. Negative COX-2 expression correlates with improved radiosensitivity and reduced inflammation.	Targeting the COX-2/PGE2 axis, including AHR inhibition, could suppress inflammation-driven tumor progression and enhance radiosensitivity.	[55–57]
Cytokines (IL-6, IL-10)	IL-6 drives ESCC progression via EGFR and STAT3 signaling, enhancing proliferation, invasion, and stemness. IL-10 promotes immune evasion by upregulating PD-L1 and Met signaling, contributing to an immunosuppressive microenvironment that enhances tumor progression.	Blocking IL-6/STAT3 and IL-10/PD-L1 pathways may improve anti-tumor immunity and reduce inflammation-driven tumor progression.	[58–61]
Immune Cell Interactions	Tumor cells secrete cytokines and chemokines that recruit immunosuppressive immune cells (TAMs, Tregs, MDSCs), enhancing tumor growth and immune evasion. TAMs secrete IL-10 and TGF-β, suppressing cytotoxic T cells and promoting angiogenesis.	Modulating immune cell recruitment, such as targeting TAM-derived CCL22/CCR4-FAK signaling, may reprogram the inflammatory TME and enhance therapy efficacy.	[62–64]

therapy.[69] Additionally, LAMC1 serves as a potential biomarker and therapeutic target in ESCC by promoting tumor proliferation and migration via Akt–NFκB–MMP9/14 signaling and inducing an inflammatory TME through CXCL1-mediated iCAF formation.[53] Moreover, IL-1β-driven chronic inflammation promotes ESCC development in L2-IL-1β transgenic mice, characterized by increased inflammatory biomarkers, including T cell infiltration, iNOS, and pro-inflammatory cytokines, highlighting IL-1β as a key mediator in ESCC pathogenesis.[70] IL-10 also modulates the immunosuppressive microenvironment in ESCC by downregulating PD-L1 expression via the Met signaling pathway, highlighting IL-10 as a key inflammation biomarker in ESCC pathogenesis.[60] Hypomethylation-driven upregulation of PLCE1 activates the NF-κB signaling pathway in ESCC, promoting angiogenesis and tumor progression, highlighting PLCE1 as a key inflammation biomarker and potential therapeutic target.[71] Peripheral blood VEGF and inflammation biomarkers (CLR and GPS) serve as key predictors of clinical response and prognosis in non-operative ESCC, providing a reliable inflammation-based biomarker model for patient evaluation.[72] These biomarkers (Table 2) not only provide mechanistic insights into ESCC but also represent potential therapeutic targets and prognostic indicators, guiding personalized treatment strategies.

RT in ESCC

RT is a cornerstone in the treatment of ESCC, utilized in neoadjuvant, definitive, and palliative settings. Despite its effectiveness, RT faces significant challenges, including tumor resistance and its impact on the TME. Advancements in the understanding of RT-induced tumor cell death, immunomodulation, and resistance have facilitated the development of optimized strategies to enhance therapeutic efficacy and improve patient outcomes.

Table 2 Inflammation-Related Biomarkers in ESCC

Inflammatory Biomarker	Function in ESCC	Reference
CRP	Marker associated with poor prognosis, advanced tumor stage, and lymph node metastasis	[65]
IL-6	Promotes tumor progression via STAT3 signaling and systemic inflammation	[66]
IL-8	Activates STAT3 and promotes immune suppression and metastasis	[67, 68]
NLR	Reflects immune imbalance and predicts resistance to therapy	[69]
LAMC1	Induces tumor growth and inflammatory CAFs via Akt–NF-κB–CXCL1–STAT3 axis	[53]
IL-1β	Drives chronic inflammation and T cell infiltration; enhances cytokine production	[70]
IL-10	Suppresses immunity via PD-L1/Met pathway; contributes to inflammation	[60]
PLCE1	NF-κB activation via hypomethylation; promotes angiogenesis and growth	[71]
VEGF	Serum marker correlated with poor prognosis in non-operative ESCC	[72]
CLR	RT-end biomarker indicating poor prognosis	[72]
GPS	Predictive of outcomes 3 months post-RT	[72]

RT as a Standard Treatment for ESCC

RT is employed across multiple treatment settings in ESCC. In the neoadjuvant setting, RT is frequently combined with chemotherapy to reduce tumor burden and enhance surgical resectability.[73] Neoadjuvant CRT has been shown to significantly improve survival in locally advanced ESCC, leading to improved long-term outcomes.[74] The definitive RT, often in combination with chemotherapy, serves as a primary treatment approach for patients who are ineligible for surgery. In advanced or metastatic ESCC, palliative RT is utilized to relieve symptoms such as dysphagia and pain.[75]

The efficacy and safety of RT are influenced by dose fractionation strategies. Conventional fractionation involves daily doses of 1.8–2.0 Gy, with a total dose of 50–60 Gy administered over 5–6 week.[76] Hypofractionated radiotherapy (HFRT), delivering higher doses per fraction over a shorter treatment duration, has gained attention for its potential to improve tumor control while reducing treatment time.[77] HFRT has been shown to enhance local tumor control in ESCC while maintaining an acceptable toxicity profile.[78] Adaptive RT, which tailors treatment based on tumor response, has also emerged as a promising strategy to minimize radiation exposure to healthy tissues.[79]

RT-Induced Effects on Cancer and the TME

RT exerts its anti-tumor effects primarily by inducing DNA damage, leading to tumor cell death through apoptosis, necrosis, or mitotic catastrophe. Double-strand breaks (DSBs) represent the most lethal form of DNA damage, with repair mediated by pathways such as non-homologous end joining (NHEJ) and homologous recombination (HR).[80] RT-induced double-strand breaks activate the ATM/ATR pathway, coordinating DNA repair and cell cycle arrest. However, cancer cells frequently exploit these repair mechanisms to evade RT-induced lethality, contributing to treatment resistance.[81]

Beyond direct cytotoxicity, RT influences the immune response, making it a potential ally in immunotherapy. Radiation-induced ICD plays a key role in stimulating anti-tumor immunity by releasing damage-associated molecular patterns (DAMPs) such as calreticulin and ATP, which activate dendritic cells (DCs) and enhance T cell-mediated tumor eradication.[82] RT-induced immunogenic cell death has been associated with improved survival outcomes in ESCC patients receiving immunotherapy.[83] RT also facilitates tumor antigen release, allowing DCs to present antigens to T cells and generate a systemic immune response.[84] This phenomenon, known as the abscopal effect, has been observed in ESCC patients treated with RT in combination with ICIs.[85] However, RT can also induce immune suppression by upregulating PD-L1 and CTLA-4 expression in the TME, thereby limiting its immunostimulatory effects.[86,87]

Limitations and Resistance Mechanisms

Hypoxia is a major factor contributing to RT resistance in ESCC. Tumor hypoxia reduces the generation of reactive oxygen species (ROS), which are essential for mediating RT-induced DNA damage.[88] HIF-1α, a central regulator of hypoxic responses, enhances radio resistance by upregulating DNA repair pathways and promoting angiogenesis.[4]

Targeting HIF-1α with small-molecule inhibitors has been shown to enhance the efficacy of RT in hypoxic ESCC tumors.[89]

Cancer cells employ multiple mechanisms to evade RT-induced cell death, including activation of DNA repair pathways. The ATM/ATR pathway is critical for detecting and repairing DSBs, while PARP and Ku70/80 facilitate the repair of single-strand breaks (SSBs) and NHEJ, respectively.[90] PARP inhibitor olaparib enhances the efficacy of proton beam therapy in platinum- and radiation-resistant ESCC by promoting DNA double-strand breaks and impairing homologous recombination repair.[91] Similarly, targeting ATM/ATR with specific inhibitors has demonstrated potential in overcoming radioresistance.[92]

The TME further contributes to RT resistance through complex interactions between cancer cells and stromal components. CAFs secrete cytokines such as TGF-β and IL-6, which promote cancer cell survival and enhance stemness.[93,94] CAF-secreted PAI-1 and TGF-β promote ESCC cell migration and invasion through the AKT and ERK1/2 pathways, and may enhance radio resistance via exosomal miR-3656 targeting the ACAP2/PI3K-AKT axis.[95–97] TAMs, particularly those with an M2 phenotype, also contribute to radio resistance by secreting pro-survival factors and suppressing anti-tumor immunity.[98] Targeting TAMs with CSF-1R inhibitors has been shown to enhance the efficacy of RT in ESCC.[99]

Inflammation and TME Modulation in Response to RT

RT exerts its therapeutic effects not only by directly eradicating cancer cells but also by reshaping the TME and modulating systemic immune responses. While RT can stimulate pro-inflammatory and immunogenic effects, it can also induce immunosuppressive mechanisms that contribute to resistance. Understanding the dual role of RT in inflammation and TME modulation is essential for optimizing its therapeutic efficacy in ESCC.

RT-Induced Inflammation

RT triggers a robust inflammatory response in the TME, characterized by the upregulation of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[100] These cytokines have complex roles in tumor progression and immune modulation. IL-6 promotes cancer cell survival and angiogenesis via STAT3 activation, while TNF-α, despite its apoptotic potential, can also contribute to tumor progression by activating NF-κB signaling.[101–103] RT-induced IL-1β secretion has been shown to facilitate the recruitment of MDSCs into the TME, exacerbating immune suppression.[104]

The balance between pro-inflammatory and anti-inflammatory responses following RT significantly influences treatment outcomes. While RT initially induces a pro-inflammatory state, it can also activate immunosuppressive pathways, including the upregulation of TGF-β and IL-10, which inhibit anti-tumor immunity.[105] The TGF-β pathway has been identified as a key mediator of RT-induced immune suppression, with its inhibition shown to enhance RT efficacy in ESCC. TGF-β signaling plays a central role in promoting radio resistance in ESCC by inducing epithelial-mesenchymal transition (EMT) through Smad2/3 phosphorylation and E-cadherin suppression,[106] activating CAF-mediated expression of EMT markers such as Slug, Snail, and Zeb1,[107] enhancing tumor progression via paracrine signaling from CAFs,[96] and contributing to immune suppression by stimulating MDSC production through IL-6/exosomal miR-21 pathways.[108] Notably, inhibition of TGF-β signaling using DNMT inhibitors sensitizes ESCC cells to RT by inducing G2/M cell cycle arrest and apoptosis.[109]

Additionally, RT can induce IL-10 expression in tumor-associated macrophages as part of a feedback mechanism involving HMGB1/TNF-α signaling, which activates downstream STAT3 pathways, thereby suppressing antigen presentation and T cell activation within the TME.[110,111]

Immune Modulation by RT

The abscopal effect describes a phenomenon in which RT elicits systemic anti-tumor immunity, leading to regression of tumors outside the irradiated field.[112] This effect is mediated by the release of tumor antigens and DAMPs which activate DCs and promote T cell-mediated tumor clearance.[113] RT-induced calreticulin exposure on cancer cells has been shown to enhance DC activation and antigen cross-presentation, facilitating a systemic immune response.[114] However, the abscopal effect remains rare, likely due to the highly immunosuppressive TME in ESCC.

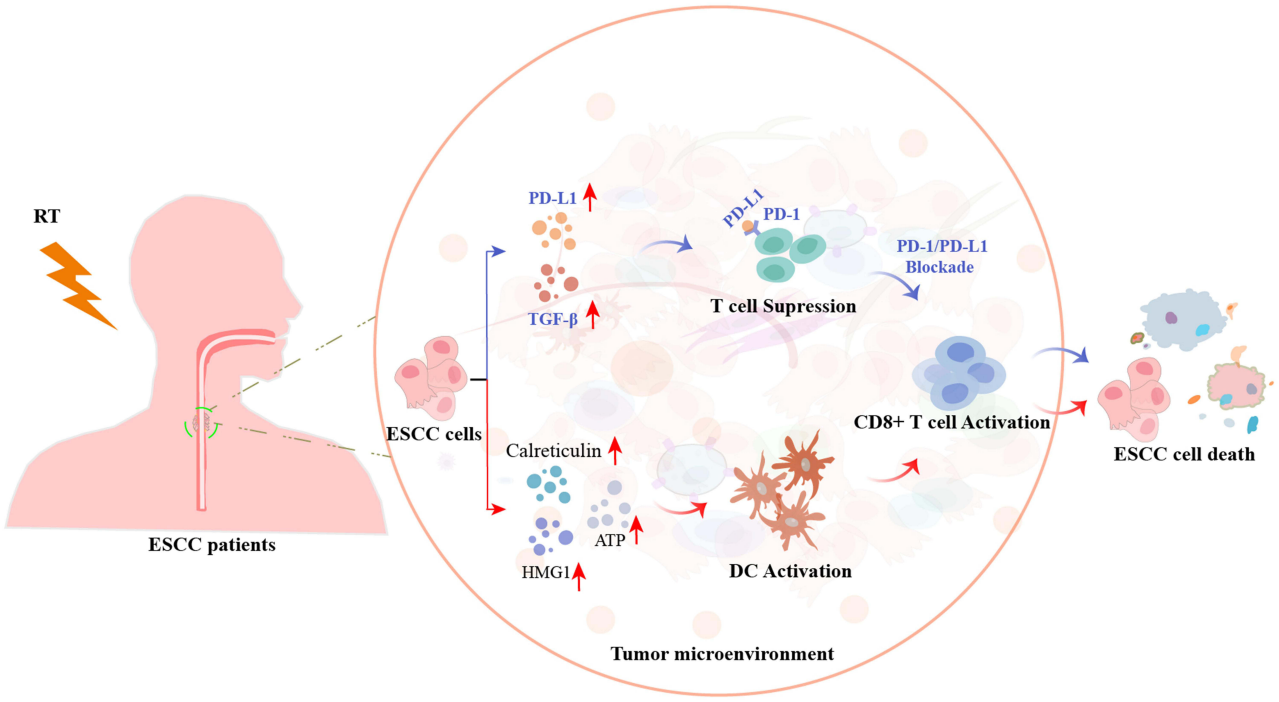

Figure 2 Interplay Between RT and Immunotherapy in ESCC. The dual role of RT and its synergy with ICIs in the ESCC TME. RT induces tumor cell death and ICD, releasing DAMPs such as calreticulin, HMGB1, and ATP, that activate DCs and initiate antitumor T cell responses. However, RT also upregulates immunosuppressive factors such as PD-L1 and TGF-β, contributing to T cell suppression. The addition of PD-1/PD-L1 blockade restores T cell function, enhancing $CD8^+$ T cell activation and systemic immunity.

While RT can activate anti-tumor immunity, it also contributes to immune exhaustion by upregulating immune checkpoint molecules such as PD-L1 and CTLA-4. RT-induced PD-L1 expression on cancer cells and TAMs inhibits T cell activity, diminishing the effectiveness of RT.[115] Similarly, upregulation of CTLA-4 on Tregs has been implicated in RT-induced immune suppression.[116] Combining RT with ICIs has shown promise in overcoming these limitations and potentiating anti-tumor immunity.[117] The bidirectional interactions between RT and immune response in ESCC are summarized in Figure 2.

Combination Approaches Targeting Inflammation and the TME

Targeting RT-induced inflammation with anti-inflammatory agents has emerged as a promising strategy to enhance RT efficacy. NSAIDs and COX-2 inhibitors reduce the production of pro-inflammatory cytokines and prostaglandins, mitigating RT-induced inflammation and tumor progression.[118,119] COX-2 inhibitors enhance the efficacy of RT in ESCC by suppressing PGE2 production and inhibiting NF-κB signaling, thereby reducing inflammation, and improving tumor radiosensitivity.[49] Although NSAIDs can reduce IL-6 levels and attenuate inflammation, their suppression of PGE2 may inadvertently elevate TNF-α production, highlighting the need to balance pro- and anti-inflammatory effects when combining NSAIDs with RT to optimize therapeutic outcomes.[120]

Modulating the TME to overcome RT resistance is another promising therapeutic strategy. TGF-β inhibitors counteract the immunosuppressive effects of TGF-β, enhancing T cell infiltration and activation within the TME.[28] The combination of RT with TGF-β inhibition has been shown to improve tumor control and prolong survival in ESCC.[11] VEGF blockade promotes vascular normalization and alleviates tumor hypoxia, thereby enhancing RT efficacy through improved oxygenation and modulation of the TME.[121] Targeting VEGF enhances RT sensitivity in ESCC, as VEGF knockdown improves tumor cell responsiveness to RT and elevated serum VEGF levels correlate with poor clinical outcomes, supporting VEGF inhibition as a potential radio-sensitization strategy.[122] Key strategies to improve RT outcomes in ESCC are summarized in Table 3.

Table 3 Therapeutic Strategies to Enhance RT Efficacy in ESCC

Strategy Type	Example Targets	Mechanism of Action	Impact on RT Efficacy	References
ICIs	Anti-PD-1, Anti-PD-L1	Reverses T cell exhaustion and boosts systemic immunity	Enhances systemic immunity	[123–127]
Anti-inflammatory Therapy	NSAIDs, COX-2 inhibitors	Suppresses IL-6, TNF-α, and PGE2; blocks NF-κB signaling	Improves radiosensitivity	[49, 118–120]
TME-targeting Therapy	Anti-TGF-β, Anti-VEGF	Reduces immunosuppression, improves oxygenation	Reduces immunosuppression	[28, 105, 106, 121, 122]
Metabolic Inhibition	Glycolysis or lipid inhibitors	Disrupts tumor energetics and redox stability	Disrupts adaptive resistance	[14, 114–117]
AI-guided RT Planning	AI/ML prediction models	Predicts dose/toxicity and personalizes delivery	Optimizes RT delivery	[15, 16, 128]

Therapeutic Implications and Future Directions

The intricate interplay between inflammation, TME, and RT in ESCC has paved the way for novel therapeutic strategies. Integrating immunotherapy with RT, targeting inflammatory pathways and the TME, and leveraging advanced technologies such as AI are transforming treatment approaches. These advancements hold the potential to improve therapeutic efficacy and personalize treatment for ESCC patients.

Integrating Immunotherapy with RT

The combination of ICIs with RT represents a promising strategy for enhancing anti-tumor immunity in ESCC. PD-1/PD-L1 inhibitors disrupt the interaction between PD-1 on T cells and PD-L1 on tumor cells, thereby restoring T cell function and promoting tumor elimination.[123,124] RT has been shown to augment the efficacy of ICIs by inducing ICD and releasing tumor antigens, which facilitate DC activation and subsequent T cell priming.[84,129] In ESCC, RT combined with anti-PD-1 therapy (camrelizumab) enhances peripheral $CD8^{+}$T cell activation and more effectively reshapes memory T cell differentiation than CRT, contributing to improved prognosis in patients with locally advanced ESCC.[125] Furthermore, Integrating PD-1/PD-L1 inhibitors with RT enhances antitumor immunity in ESCC by promoting tumor antigen release, increasing PD-L1 expression, and facilitating T cell activation through modulation of the TME and reversal of immune exhaustion.[126,127]

Personalized RT strategies, tailored to individual tumor biology and patient characteristics, are essential for optimizing outcomes. Advances in molecular profiling and imaging have facilitated the development of adaptive RT, which dynamically adjusts treatment plans based on tumor response and alterations in the TME.[128] Hypofractionated RT delivers higher doses per fraction over a shorter treatment course and has been shown to improve tumor control while maintaining a favorable toxicity profile in ESCC.[130] Additionally, radiogenomics integrates genomic data into RT planning and is emerging as a tool for identifying patients most likely to benefit from RT-ICI combination therapy.[131]

PD-1/PD-L1 inhibitors have demonstrated encouraging results in ESCC, particularly when combined with RT, by enhancing T cell-mediated antitumor responses and overcoming immune suppression.[132] However, these agents represent only part of the evolving immunotherapeutic landscape. Newer checkpoint targets such as lymphocyte-activation gene 3 (LAG-3) and T cell immunoglobulin and mucin-domain containing-3 (TIM-3) are emerging as potential immunomodulatory regulators in ESCC, with early evidence suggesting they may mediate resistance to PD-1 blockade and contribute to immune escape.[133,134] Thus, dual or sequential blockade strategies involving PD-1 and LAG-3 or TIM-3 warrant exploration in combination with RT. Additionally, while COX-2 inhibitors have been proposed to augment radiosensitivity by suppressing inflammation, recent findings from the CHECKRT trial reported no significant clinical benefit of COX-2 inhibition in radio sensitizing ESCC.[12] This underscores the necessity of critically assessing the translational potential of inflammation-targeted therapies. Overall, while PD-1/PD-L1 inhibitors remain the most established class in immunoradiotherapy for ESCC, broadening the scope to include alternative checkpoints and negative findings is crucial for a balanced and comprehensive view of immunotherapeutic strategies. Table 4 summarizes selected phase II trials evaluating radiotherapy combined with ICIs in ESCC.

Table 4 Selected Phase II Trials Evaluating Radiotherapy Combined with ICIs in ESCC

ICI Agent	RT Setting	Patient Population	Key Outcomes	Reference
PD-1 Inhibitor	Definitive RT	ESCC with immune nutrition support	ORR improved; PFS prolonged	[32]
Camrelizumab + Irinotecan	Palliative RT	Oligometastatic ESCC post-1L failure	PR 58.3%, median PFS 6.3 months	[33]

Targeting Inflammatory Pathways and the TME in ESCC

Targeting the TME with emerging therapeutic agents offers new opportunities to overcome resistance and enhance RT efficacy. CXCR4 inhibitors disrupt the interaction between CXCR4 on tumor cells and CXCL12 within the TME, thereby limiting tumor cell migration and metastasis.[135] CXCR4 blockade has been shown to enhance RT-induced tumor cell death and stimulate immune activation in ESCC.[11] Similarly, inhibition of TGF-β, a key immunosuppressive cytokine in the TME, promotes T cell infiltration and enhances anti-tumor immunity.[136] Combining RT with TGF-β blockade can be used to improve tumor control and prolong survival in ESCC models.[11] Moreover, repositioning anti-inflammatory drugs such as NSAIDs and selective COX-2 inhibitors offers a cost-effective strategy to counteract RT-induced inflammation. They suppress the release of prostaglandins and cytokines like IL-6 and TNF-α, reduce PGE2 levels, and inhibit NF-κB signaling, collectively mitigating inflammation-driven resistance and improving RT outcomes in ESCC.[49,118–120]

Beyond classical cytokines such as IL-6 and TNF-α, recent studies have identified the NLRP3 inflammasome as a critical mediator of RT-induced inflammation in ESCC. German groups have demonstrated that NLRP3 activation contributes to immune suppression and treatment resistance in preclinical ESCC models, suggesting that NLRP3-targeted therapies may enhance RT efficacy.[137]

Translational Outlook

Advanced computational strategies, including AI-driven RT (AI-RT), are transforming precision oncology. While several models have emerged from East Asian institutions, notable innovations have also been developed in Western settings. For instance, researchers at Memorial Sloan Kettering Cancer Center (MSKCC) in the United States have proposed machine learning-based dose prediction models to optimize target coverage and minimize toxicity in ESCC.[138] Additionally, global collaborations such as the NRG Oncology Phase III hypofractionation trials offer valuable insights into RT design and outcomes in multinational ESCC cohorts.[139]

Despite promising preclinical results, AI-based RT strategies face deployment challenges including image standardization, algorithm reproducibility, and integration into clinical workflows.[138] These barriers highlight the need for rigorous validation and platform harmonization before widespread clinical implementation.

In parallel, recent findings on STING (stimulator of interferon genes) agonists suggest potential synergy with RT in reversing immune suppression and enhancing dendritic cell priming. Incorporating STING-RT combinations into ESCC treatment paradigms may potentiate antitumor immunity and deserves further investigation.[99]

RT elicits divergent effects on the TME, ranging from immune activation to profound immunosuppression. These opposing responses are shaped by cytokine release, immune cell infiltration, and the nature of RT delivery. To clarify these context-specific dynamics, Table 5 presents a comparative overview of pro-inflammatory versus immunosuppressive TME features after RT in ESCC. This table summarizes the distinct immunological profiles observed after RT in ESCC, comparing pro-inflammatory and immunosuppressive responses. These include key cytokines, immune cell subsets, molecular drivers, RT parameters, and associated biomarkers. The immunological outcome of RT is context-dependent and may influence sensitivity to immune checkpoint blockade or the need for combinatory interventions.This framework supports the rationale for tailoring combination therapies based on immune phenotype and radiation dose/fractionation strategies.

Statistical Considerations

To strengthen translational validity, future analyses of inflammatory biomarkers such as CRP and IL-6 should employ multivariate Cox proportional hazards models to adjust for potential confounding variables, including smoking history,

Table 5 Contrasting Immune Networks in the TME Following RT in ESCC

Feature	Pro-inflammatory Network	Immunosuppressive Network	Reference
Dominant Cytokines	IL-6, TNF-α, IL-1β	TGF-β, IL-10	[24–28, 58–61, 86]
TME Characteristics	Inflammation-driven, immune activation	Immune exclusion, stromal remodeling	[3, 53, 96]
Key Immune Cells	$CD8^+$ T cells, dendritic cells	Tregs, MDSCs, TAMs	[62–64, 82, 84]
Molecular Drivers	NF-κB, STAT3, COX-2/PGE2 axis	TGF-β signaling, CAF-derived PAI-1, IL-6/miR-21	[47–57, 105–108]
RT Parameters	Fractionated RT, moderate dose	SBRT, high-dose RT increasing TGF-β	[24–28]
Therapeutic Implications	Enhances ICI response, promotes antigen presentation	Induces checkpoint expression, T cell exhaustion	[84, 126–128]

human papillomavirus status, and tumor stage. Reliance on univariate analyses may lead to overestimation of effect sizes and misidentification of independent predictors of RT response.[140] AI and machine learning applications in RT planning should adhere to established methodological frameworks, such as the TRIPOD reporting standards. Comprehensive reporting of model validation procedures, cross-validation strategies, and performance metrics, including area under the receiver operating characteristic curve with confidence intervals, is essential to ensure robustness and reproducibility in clinical implementation.[141]

In preclinical mechanistic studies, the use of underpowered statistical comparisons should be supplemented with appropriate corrections for multiple hypothesis testing, such as false discovery rate control or family-wise error rate adjustment, to mitigate the risk of spurious findings.[140]

Furthermore, claims regarding survival benefits from combined therapeutic regimens should be substantiated by quantitative measures, including hazard ratios, time-specific survival analyses, absolute risk reduction, and number needed to treat, to facilitate rigorous clinical extrapolation and inform future trial designs RT.[142]

As this is a narrative review, statistical metrics such as AUC with 95% confidence intervals and hazard ratios are discussed to highlight methodological recommendations for future studies. These metrics are not reported as original results.

Conclusion

This review highlights the central role of inflammation-driven mechanisms in shaping the TME and modulating RT responses in ESCC. Clinically validated strategies such as anti-PD-1 therapies combined with RT have demonstrated objective response rate (ORR) improvements of 20–30% in Phase II trials,[33,143] supporting their near-term translational potential. In contrast, emerging modalities like STING agonists and NLRP3 inhibitors remain in early-stage evaluation and require further validation.[144,145] Mechanistically, RT-induced cytokine release including IL-6 and TGF-β drives dynamic TME remodeling, promoting both immune activation and suppression depending on dose and fractionation. Targeting these bidirectional responses through dual checkpoint blockade, TME-modulatory agents, or radiosensitizers represents a rational path forward.

AI-driven tools, including RT planning algorithms and radiomic biomarkers, offer promising precision-guided approaches but currently face reproducibility and standardization challenges that limit clinical implementation.[146,147] Furthermore, the cost-effectiveness and access to novel immuno-radiotherapeutics remain substantial barriers, particularly in low-resource settings. To accelerate clinical translation, future work must integrate robust biomarker-guided stratification, dose-adaptive immune profiling, and comparative trials distinguishing exploratory hypotheses from validated protocols. Such integration will be essential to move beyond generalized benefits toward durable, measurable, and equitable improvements in ESCC outcomes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors report no conflicts of interest in this work.

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