



Immunotherapy and Radiotherapy: Where Do the Paths Meet?

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Abstract

Radiotherapy (RT) has traditionally been considered a local treatment; however, increasing evidence demonstrates that ionizing radiation can modulate systemic antitumor immunity. Radiation-induced tumor cell death promotes antigen release, dendritic-cell activation, major histocompatibility complex class I expression, and type I interferon signaling, potentially converting the irradiated tumor into an in situ vaccine. Immune checkpoint inhibitors (ICIs), in turn, may enhance and sustain radiation-induced antitumor immunity by overcoming T-cell exhaustion and immune suppression. This provides a biological rationale for combining RT with immunotherapy across different treatment settings. The abscopal effect, although uncommon with RT alone, has generated considerable interest in this approach. Clinically, the strongest evidence currently comes from unresectable stage III non-small-cell lung cancer (NSCLC), where consolidation durvalumab after concurrent chemoradiotherapy has established a major therapeutic paradigm. Trials evaluating concurrent and perioperative RT-ICI combinations in other malignancies are rapidly expanding. However, optimal radiation dose, fractionation, sequencing, treatment volume and patient selection remain unresolved. This review summarizes the biological basis, clinical evidence, treatment sequencing, toxicity, and future directions of combined RT and immunotherapy.

Keywords: radiotherapy; immunotherapy; immune checkpoint inhibitors; PD-1; PD-L1; abscopal effect; cGAS-STING; immunogenic cell death

Introduction

The traditional view of radiotherapy as a purely local cytotoxic treatment has evolved considerably. Radiation can influence the tumor microenvironment and activate both innate and adaptive immunity. Radiation-induced tumor cell death results in the release of tumor-associated antigens and damage-associated molecular patterns, which can stimulate antigen-presenting cells and subsequent T-cell activation [1,2].

This interaction may extend beyond the irradiated field. Activated tumor-specific lymphocytes can recognize tumor cells at distant sites, producing the clinically observed, although relatively uncommon, abscopal effect [2,3]. Immune checkpoint inhibitors

targeting programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can amplify these radiation-induced immune responses, providing a rationale for combined treatment [3,4].

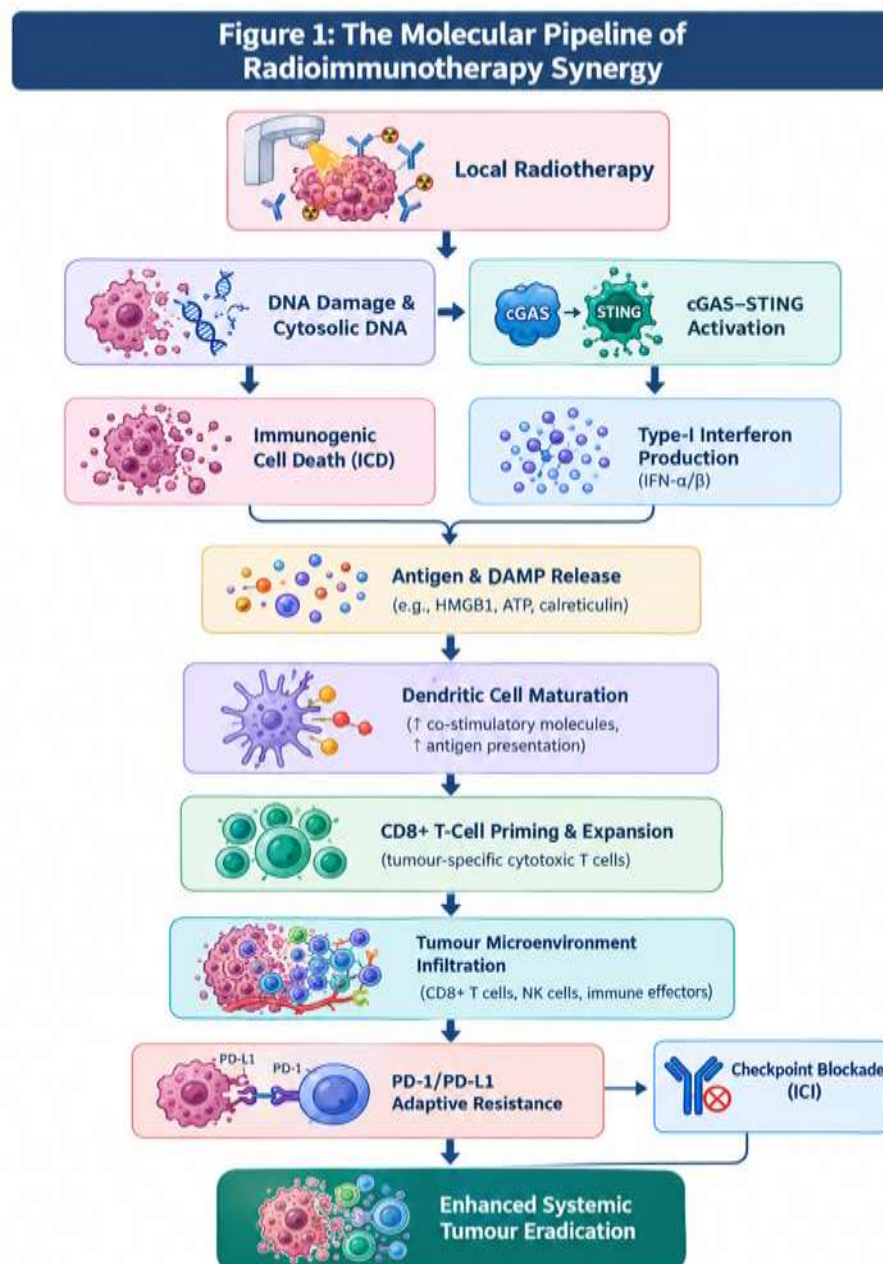
How Do Radiotherapy and Immunotherapy Interact?

Radiation can promote antitumor immunity through several interconnected mechanisms:

1. **Immunogenic cell death: Radiation causes tumor cell death with release of tumor antigens and danger-associated molecular patterns [1].**

2. **cGAS–STING activation:** Radiation-induced cytosolic DNA can activate the cGAS–STING pathway and type I interferon signaling, facilitating innate immune activation [5].
3. **Antigen presentation:** Radiation increases tumor antigen availability and can enhance dendritic-cell maturation and antigen presentation [1,5].
4. **T-cell recruitment:** Radiation-induced inflammatory signaling and chemokines facilitate infiltration of activated CD8⁺ T cells into the tumor.
5. **Checkpoint modulation:** Radiation may increase PD-L1 expression, providing a biological rationale for PD-1/PD-L1 blockade [6].
6. **Systemic immunity:** Activated tumor-specific lymphocytes may mediate immune responses at nonirradiated sites, forming the basis of the abscopal effect [2,3].

Figure 1: The Molecular Pipeline of Radioimmunotherapy Synergy



Immunotherapy, Chemotherapy and Radiotherapy: A Therapeutic Triad

Chemotherapy, RT, and immunotherapy may complement one another through partially overlapping mechanisms. Several cytotoxic agents induce immunogenic cell death, increase tumor antigen availability and modify immunosuppressive populations [7]. RT provides additional antigen release and inflammatory signaling, while ICIs remove inhibitory signals that limit T-cell activity.

This provides a rationale for integrating all three modalities, particularly in locally advanced disease. However, greater treatment intensity may also increase toxicity, and the optimal sequencing of chemotherapy, RT and immunotherapy remains disease-specific. The clinical applications and treatment sequencing are depicted in Table 1.

Table-1: Clinical Applications and Treatment Sequencing

Setting	Rationale	Representative application	Current status
Neoadjuvant	Enhance antigen release and systemic immune priming before surgery	RT ± ICI in selected locally advanced or resectable cancers	Investigational
Concurrent	Radiation-induced immune activation with simultaneous checkpoint blockade	Definitive chemoradiotherapy + ICI	Under evaluation
Consolidation after RT	Radiation is followed by sustained checkpoint inhibition after definitive chemoradiotherapy	Unresectable stage III NSCLC after definitive chemoradiotherapy	Established in appropriate patients
ICI followed by RT	RT used to augment or restore response at selected sites	Oligoprogression or limited residual disease	Increasingly used; evidence evolving
Metastatic/abscopal strategy	Irradiate selected lesion(s) to stimulate systemic immunity	SBRT + ICI	Mainly investigational

Existing Clinical Evidence

Overall, the current evidence supports a disease-specific rather than a universal approach to RT–ICI combinations. Outside established indications such as consolidation durvalumab after chemoradiotherapy in unresectable stage III NSCLC, many RT–ICI strategies should currently be regarded as investigational. The abscopal effect remains an important biological concept in this field, but clinically documented responses at distant non-irradiated sites remain uncommon and difficult to predict. Consequently, RT should not currently be administered solely with the expectation of inducing an abscopal response outside a clinical trial or carefully selected investigational setting

[2,3]. Another area of growing interest is the use of RT for oligoprogression or limited residual disease during ICI therapy. In such situations, local RT may provide control of resistant lesions while systemic immunotherapy is continued. The approach is increasingly used in selected clinical settings, but optimal patient-selection criteria and the extent to which local RT improves systemic outcomes remain subjects of ongoing investigation.

a) Non-small-cell lung cancer

The strongest clinical evidence for integration of RT and immunotherapy comes from the PACIFIC trial. Patients with unresectable stage III NSCLC without disease progression following concurrent platinum-based

chemoradiotherapy received durvalumab or placebo for up to 12 months [8].

Long-term follow-up demonstrated sustained improvement in both progression-free and overall survival. At 5 years, overall survival was 42.9% with durvalumab versus 33.4% with placebo, while 5-year progression-free survival was 33.1% versus 19.0%, respectively [9]. These findings established consolidation PD-L1 inhibition following definitive chemoradiotherapy as a major therapeutic paradigm in unresectable stage III NSCLC.

Real-world evidence has subsequently supported the feasibility and effectiveness of this approach, with PACIFIC-R reporting 5-year real-world progression-free survival and overall survival of 35.2% and 49.2%, respectively [10].

b) Other malignancies

The RT–ICI combination is being investigated extensively in head and neck, oesophageal, cervical, breast, gastrointestinal and genitourinary malignancies. The KEYNOTE-975 trial, for example, evaluates pembrolizumab combined with definitive chemoradiotherapy in locally advanced oesophageal and gastroesophageal-junction cancers [11].

Similarly, trials in head and neck cancer and other solid tumors are evaluating concurrent or perioperative immunotherapy with RT. Outside established indications such as consolidation durvalumab after definitive chemoradiotherapy in unresectable stage III NSCLC, many RT–ICI strategies should currently be regarded as investigational.

Toxicity: Where Does the Risk Lie?

Combining RT and immunotherapy may produce overlapping or additive toxicity. The pattern depends strongly on the irradiated organ and the specific immune agent.

Thoracic RT raises particular concern regarding pneumonitis. Distinguishing radiation pneumonitis from immune-mediated pneumonitis can be difficult because symptoms, imaging findings and timing may overlap [12].

Other clinically relevant toxicities include:

- mucositis and dermatitis with head and neck RT;
- oesophagitis following thoracic irradiation;
- enteritis/colitis following pelvic or abdominal treatment;
- hepatitis and endocrinopathies related to immune checkpoint blockade;
- uncommon but potentially severe myocarditis, nephritis and neurological immune-related adverse events.

Careful baseline assessment, multidisciplinary monitoring and prompt recognition of immune-related adverse events are essential.

Challenges in Clinical Implementation

Several important questions remain unresolved.

Optimal radiation dose and fractionation: Hypofractionated RT and SBRT may produce stronger immunological effects in selected settings, but the ideal dose and fractionation remain uncertain.

Treatment sequencing: Whether RT should precede, follow or coincide with immunotherapy may depend on tumor type, disease burden and immune phenotype.

Irradiated volume: Large radiation fields can cause substantial lymphocyte depletion, potentially counteracting immune activation.

Patient selection: PD-L1 expression alone is unlikely to fully predict benefit from RT–ICI combinations.

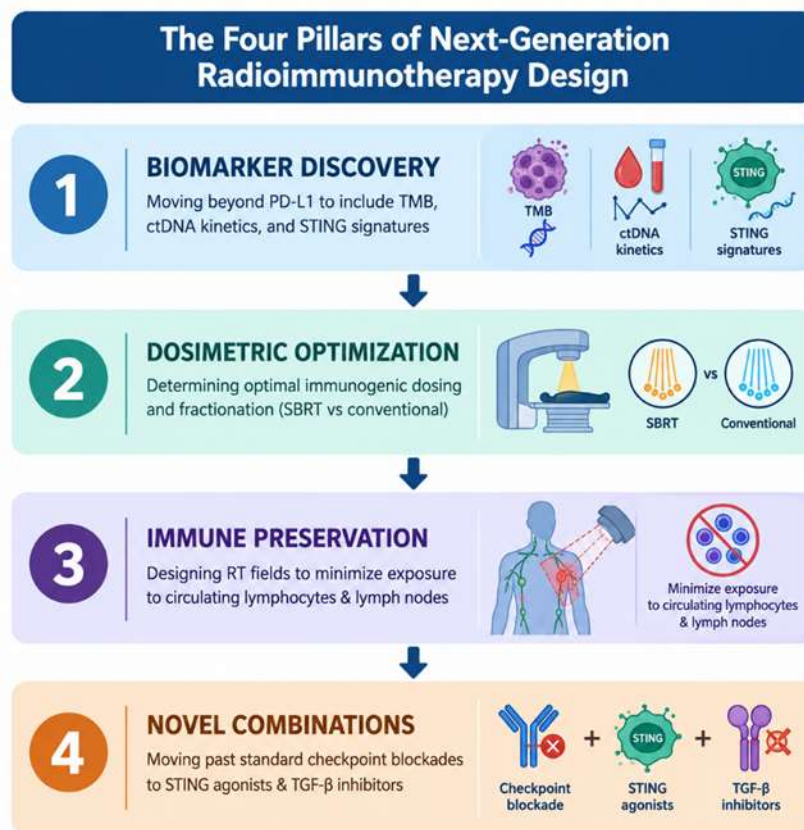
Biomarkers: Tumor mutational burden, circulating tumor DNA, immune-cell infiltration, interferon signatures and STING-pathway activity are being investigated as potential predictive biomarkers.

Toxicity: The balance between enhanced tumor control and normal-tissue toxicity remains particularly important when RT is delivered concurrently with ICIs.

Current Challenges and Future Paradigms

Despite a strong preclinical rationale, clinical trial data have shown mixed results. Achieving consistent therapeutic synergy requires addressing several key variables:

Figure 2: The Four Pillars of Next-Generation Radioimmunotherapy Design



Conclusion

Radiotherapy and immunotherapy intersect at the level of tumor cell death, antigen presentation, innate immune activation and T-cell-mediated tumor recognition. Radiation can therefore function not only as a cytotoxic treatment but also as an immunomodulatory intervention, while checkpoint inhibition can sustain and amplify radiation-induced antitumor immunity.

The clinical success of consolidation durvalumab following chemoradiotherapy in stage III NSCLC provides the clearest proof of this concept. However, the optimal dose, fractionation, sequencing, irradiated volume and biomarkers for patient selection remain uncertain in most other malignancies.

Future clinical trials should therefore move beyond simply asking whether RT and immunotherapy can be combined and instead determine which patients, radiation strategies, and treatment sequences can maximize therapeutic benefit while maintaining acceptable toxicity.

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