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From resistance to response: the immunologic awakening induced by stereotactic radiotherapy in PD-L1-negative lung cancer — a new paradigm in the management of immunologically cold NSCLC

Abstract

PD-L1-negative metastatic non-small cell lung cancer (NSCLC) remains one of the most formidable challenges in thoracic oncology. These "immunologically cold" tumors, devoid of significant PD-L1 expression and typically characterized by a non-inflamed microenvironment, have historically been resistant to immune checkpoint inhibition. Yet, a paradigm shift is underway. Stereotactic body radiation therapy (SBRT), traditionally confined to local control, has emerged as an immune potentiator capable of transforming the tumor microenvironment. SBRT induces immunogenic cell death, enhances antigen presentation, and promotes systemic immune activation, thereby priming even PD-L1-negative tumors to respond to immunotherapy.

This review integrates mechanistic insights and clinical data supporting the combination of SBRT and immunotherapy in PD-L1-negative NSCLC. It explores key randomized trials (PEMBRO-RT, Alliance A082002),[1] meta-analyses, and translational studies, and contextualizes them within the evolving understanding of the oligometastatic state. The evidence suggests that radiation, once purely cytotoxic, now occupies a new role as an immunologic adjuvant, redefining treatment frontiers for immunologically cold NSCLC.

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Adrian P Hunis
School of Medicine, Universidad de Buenos Aires (UBA), Emeritus Member of ASCO, Emeritus Member of ESMO, Honorary Member of AMA, Argentina

Correspondence: Adrian P Hunis, School of Medicine, Universidad de Buenos Aires (UBA), Emeritus Member of ASCO, Emeritus Member of ESMO, Honorary Member of AMA, Argentina

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Introduction

The advent of immune checkpoint inhibitors (ICIs) revolutionized the management of advanced NSCLC. However, the therapeutic success of ICIs has been largely restricted to tumors expressing PD-L1 or harboring a high tumor mutational burden (TMB). For PD-L1-negative patients, outcomes remain suboptimal, with median overall survival (OS) often below 12 months, even in the era of chemoimmunotherapy.

The biological basis for this resistance is multifactorial: low neoantigen expression, minimal T-cell infiltration, and the presence of an immunosuppressive tumor microenvironment (TME) dominated by regulatory T cells and myeloid-derived suppressor cells (MDSCs). Collectively, these features create an "immune desert," where checkpoint inhibition alone cannot activate meaningful antitumor responses.

Enter SBRT — a modality that delivers high doses of radiation with sub-millimetric precision in few fractions (commonly 8–10 Gy × 3). Beyond its capacity for local control, SBRT induces profound systemic immune modulation. By promoting immunogenic cell death and releasing tumor-associated antigens, SBRT can transform an immunologically inert tumor into an immune-responsive one. This transformation—termed "the immunologic awakening"—represents a new frontier in the management of PD-L1-negative NSCLC.

The biological rationale: radiation as an immune catalyst

Immunogenic cell death and DAMP release

Radiation-induced cell death is not merely apoptotic; it is profoundly immunogenic. SBRT induces DNA double-strand breaks leading to the exposure of calreticulin, release of ATP, and secretion of high-mobility group box 1 (HMGB1). These damage-associated molecular patterns (DAMPs) serve as "danger signals," alerting the immune system and promoting dendritic cell maturation and antigen presentation.

Activation of the cGAS–STING pathway

Cytosolic DNA fragments from irradiated tumor cells activate the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, inducing a surge of type I interferons. These interferons attract and activate CD8+ cytotoxic T lymphocytes (CTLs), amplifying systemic antitumor immunity (Figure 1).

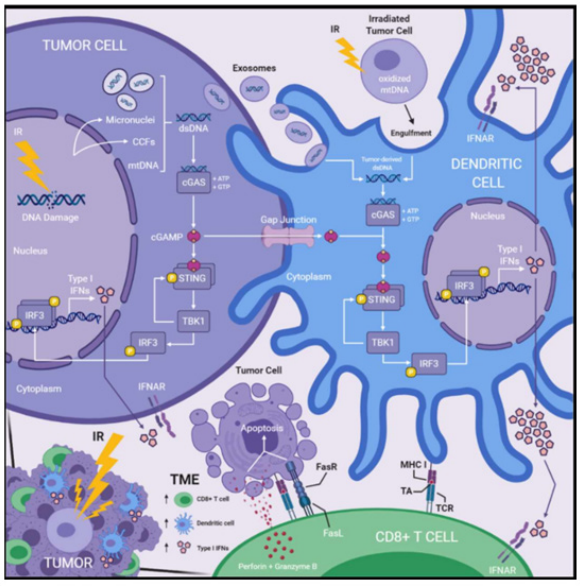

Figure 1 Mechanistic overview of SBRT-induced immune activation.

A schematic representation showing radiation-induced DNA damage, cGAS-STING activation, type I IFN release, and dendritic cell–mediated T-cell priming leading to abscopal responses.

Upregulation of PD-L1 and antigen presentation machinery

Interestingly, SBRT transiently upregulates PD-L1 and major histocompatibility complex (MHC) class I molecules on tumor cells, rendering them more susceptible to checkpoint blockade. This paradoxical PD-L1 upregulation creates an opportunity for ICIs to act synergistically, transforming a resistant tumor into a susceptible target.

Clinical evidence supporting SBRT–immunotherapy synergy

The PEMBRO-RT trial

The PEMBRO-RT study was a landmark randomized phase II trial comparing pembrolizumab alone versus pembrolizumab plus SBRT (8 Gy × 3 fractions) to a single metastatic lesion in patients with advanced NSCLC.[2]

a. Results: The combination doubled median PFS (6.6 vs. 1.9 months) and significantly improved OS (15.9 vs. 7.6 months).

b. Subgroup analysis: The greatest benefit occurred among PD-L1-negative patients, suggesting radiation may convert an immunologically cold phenotype into a responsive one.

Meta-analyses and cohort studies

Multiple meta-analyses and real-world cohorts corroborate these findings, consistently showing that RT plus ICIs improve PFS and OS compared to ICIs alone.[3–6] Importantly, concurrent or sequential SBRT administered within 2–4 weeks of ICI initiation yields the most potent immune activation (Table 1).[7-9]

The oligometastatic paradigm: a biological and therapeutic bridge

The concept of oligometastatic disease, introduced by Hellman and Weichselbaum,[10] describes an intermediate state of limited metastatic spread — typically ≤5 lesions in ≤3 organs — representing a transitional phase between localized and widespread disease. This paradigm challenges the traditional binary classification of cancer as "localized" or "metastatic."

Table 1 Key Trials Evaluating RT + ICI in Advanced NSCLC

Study	Design	RT Regimen	ICI Used	Key Findings	PD-L1-Negative Outcome
PEMBRO-RT	Phase II	8 Gy × 3	Pembrolizumab	↑ PFS, ↑ OS	Strongest benefit
DETERRED	Phase II	24 Gy/3 fractions	Durvalumab	Safe, ↑ immune activation	Positive trend
PembroX	Retrospective	Variable SBRT	Pembrolizumab	↑ response rate	Improved OS
Alliance A082002	Phase III (ongoing)	8 Gy × 3	Systemic ± ICI	Primary: OS, PFS	Pending

In NSCLC, the oligometastatic model has been validated by several randomized trials:

a. Gomez et al., Lancet Oncol 2016: Local consolidative therapy (LCT) with RT or surgery improved median PFS (14.2 vs. 4.4 months) and OS (41.2 vs. 17 months).[8]

b. Iyengar et al., JAMA Oncol 2018: Consolidative SBRT prolonged both PFS and OS in patients responding to initial chemotherapy.[9]

These findings confirm that a subset of metastatic NSCLC behaves more indolently and remains potentially curable with aggressive local therapy.

When integrated with immunotherapy, this paradigm takes on new meaning. SBRT not only eradicates visible lesions but also amplifies systemic immune responses, potentially sterilizing microscopic disease elsewhere. In this sense, SBRT serves as both a local consolidative tool and an immunologic amplifier — a bridge between cytotoxic precision and systemic control (Figure 2).

A conceptual gradient from localized to polymetastatic disease, illustrating where SBRT and immunotherapy synergy is most effective.

ASCO 2025 living guideline and clinical integration

The ASCO Living Guideline[7] for Stage IV NSCLC underscores the centrality of chemoimmunotherapy for PD-L1-negative tumors but acknowledges that local consolidative radiotherapy (LCT) can be considered in select patients with limited metastases and sustained response to systemic therapy.

This inclusion reflects a growing consensus that combining systemic and local modalities is no longer experimental but an emerging standard.

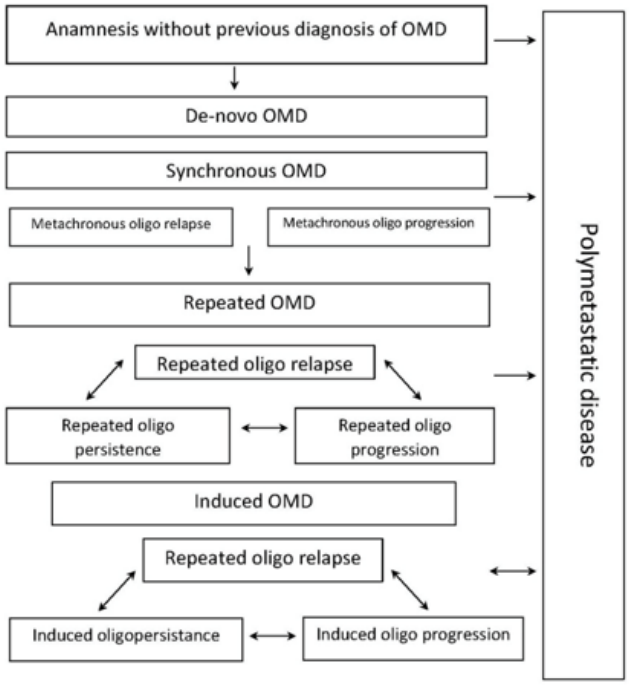

Figure 2 The Oligometastatic Spectrum and Therapeutic Opportunities.

In practice, optimal candidates are those with:

a. Controlled systemic disease,

b. 1–5 residual metastases,

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c. ECOG performance status 0–1,

d. Adequate pulmonary reserve for SBRT.

Mechanistic insights: the abscopal effect and immune reprogramming

The abscopal effect—tumor regression outside the irradiated field—was once anecdotal but is now mechanistically explained. SBRT acts as an in situ vaccine, generating systemic immunity via antigen release, dendritic activation, and T-cell proliferation.

This phenomenon underscores the spatial nature of immune control in cancer: a local event can recalibrate systemic immunity.

Ongoing translational analyses from Alliance[1] A082002 and PEMBRO-RT are mapping immune signatures predictive of response, including:

a. T-cell receptor (TCR) clonality expansion,

b. Upregulation of interferon-gamma signaling,

c. Circulating tumor DNA (ctDNA) reduction post-SBRT.

A simplified diagram showing local irradiation leading to antigen release, dendritic priming, and systemic T-cell trafficking (Figure 3).

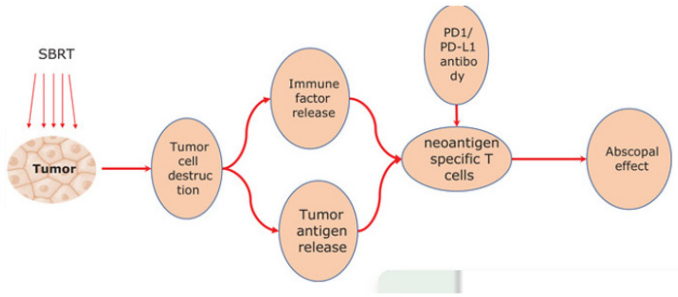

Figure 3 The Abscopal Mechanism in SBRT + Immunotherapy.

Challenges and future directions

Despite enthusiasm, several challenges remain:

a. Optimal sequencing: Whether concurrent or sequential SBRT yields superior immune synergy remains unclear.

b. Toxicity: Pneumonitis risk increases when combining thoracic RT and ICIs; careful dosimetric planning is crucial.

c. Biomarkers: PD-L1 alone is insufficient; emerging predictors include TMB, interferon signatures, and T-cell inflamed gene expression profiles.

d. Trial design: Future studies must stratify by PD-L1 status and metastatic burden to refine patient selection (Table 2).

Table 2 Ongoing Randomized Trials Exploring SBRT–ICI in PD-L1-Negative NSCLC

Trial	Phase	Treatment	Population	Key Objective
Alliance A082002	II/III	SBRT + Systemic vs Systemic alone	PD-L1 <1%	OS, PFS
NCT04013542	II	Durvalumab ± SBRT	PD-L1-negative	Immune activation
NCT03801902	II	Pembrolizumab + SBRT	Oligometastatic NSCLC	Biomarker discovery

Conclusion

Stereotactic body radiation therapy has transcended its traditional role as a local control modality. In PD-L1-negative NSCLC, it represents a biologic amplifier, capable of transforming immune-desert tumors into responsive ones.

By integrating precision radiation with immune checkpoint blockade, clinicians are beginning to bridge two paradigms—cytotoxic precision and systemic immunologic control.

The ongoing results of Alliance A082002 will define the durability of this synergy. Yet, even before those results mature, the biological logic is compelling: SBRT awakens the immune system where it once slept.

For the PD-L1-negative patient—a group long relegated to therapeutic futility—this union of radiation and immunology offers not just another line of therapy, but a redefinition of hope.

Acknowledgments

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Conflict of interest

The author states that he has no conflict of interest.

References

1. Alliance A082002 Trial. NCTN ClinicalTrials.gov Identifier: NCT03867175.
2. Theelen W, Dawei Chen, Vivek V, et al. Pembrolizumab with or without radiotherapy for metastatic NSCLC: PEMBRO-RT phase II trial. *J Clin Oncol*. 2021;39(6):661–671.
3. Sundahl N. Radiation therapy combined with PD-1/PD-L1 blockade: Mechanisms and clinical results. *Front Oncol*. 2020;10:575.
4. Demaria S, Formenti SC. Radiation as an immunological adjuvant: Current evidence on dose, fractionation, and sequencing. *Nat Rev Clin Oncol*. 2023;20(2):97–113.
5. Yuan Z. Efficacy and safety of combining radiotherapy and ICIs in advanced NSCLC: A meta-analysis. *Lung Cancer*. 2024;192:106–113.
6. Grassberger C. Synergistic effects of SBRT and immunotherapy in metastatic lung cancer: A pooled analysis. *Lancet Oncol.* 2024;25(5): e231–e242.
7. ASCO Living Guideline: Systemic Therapy for Stage IV NSCLC, 2025 Update. *J Clin Oncol.* 2025;43(4):420–437.
8. Gomez DR, Goerge RB, J Jack Lee, et al. Local consolidative therapy vs. maintenance in oligometastatic NSCLC: Randomized phase II study. *Lancet Oncol*. 2016;17(12):1672–1682.
9. Iyengar P, Zabi Wardak, David E, et al. Consolidative radiotherapy for limited metastatic NSCLC: Phase II randomized trial. *JAMA Oncol.* 2018;4(1):e173501.
10. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol.* 1995;13(1):8–10.

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