Synergizing Local and Systemic Therapies: Advances in Abscopal Effect-Based Strategies for Advanced Cancer

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Abstract

Background: The abscopal effect, defined as tumor regression at non-irradiated or non-treated distant sites following localized therapy, represents a paradigm-shifting phenomenon in oncology with the potential to achieve "functional cure" in advanced cancers. However, spontaneous or single-modality abscopal responses remain exceedingly rare, occurring in fewer than 10% of patients across most solid tumor types. Objective: This review systematically examines the synergistic framework of "local induction plus systemic enhancement" in driving abscopal effects, encompassing the underlying immunological mechanisms, clinical evidence, and translational prospects. Methods: We conducted a comprehensive literature search of PubMed and Web of Science databases (2015–2026), focusing on stereotactic body radiotherapy (SBRT), oncolytic viruses (OV), and interventional therapies as "inducers," and immune checkpoint inhibitors (ICI), immune-modulating chemotherapy, anti-angiogenic agents, and immune effector cell therapies (CAR-T/TCR-T) as "enhancers." Results: All three inducer modalities activate innate immunity through immunogenic cell death (ICD), yet single-agent abscopal rates remain below 15%. Upon combination with enhancers, SBRT plus ICI demonstrates the most robust evidence (abscopal rates 20–35%), while OV plus ICI shows efficacy in ICI-resistant populations (STOMP trial: 75% clinical benefit). Immune effector cell therapies, particularly CAR-T/TCR-T, represent the next-generation enhancers capable of overcoming solid tumor infiltration barriers when empowered by local treatments, with preclinical data demonstrating macrophage- and T cell-mediated abscopal responses following sCAR-T plus microwave ablation or OV plus CAR-T combinations. Conclusion: The "local induction plus systemic enhancement" framework represents a promising and evidence-supported strategy for achieving abscopal effects in clinical practice. ICI serves as the most universally applicable "accelerant," whereas CAR-T/CAR-NK/TCR-T therapies embody a highly promising future direction. Individualized decision-making based on MSI status, antigen heterogeneity, and treatment line remains the cornerstone of successful clinical

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translation.

Keywords: Abscopal effect; stereotactic body radiotherapy; oncolytic virus; interventional therapy; immune checkpoint inhibitor; CAR-T; combination therapy

1. Introduction

1.1 The Therapeutic Dilemma in Advanced Cancer

Advanced malignancies pose one of the most formidable challenges in modern oncology. Conventional systemic therapies, including cytotoxic chemotherapy and molecularly targeted agents, suffer from substantial toxicities and near-universal emergence of therapeutic resistance[1,2]. While local treatments such as surgery and radiotherapy excel at controlling localized disease, they fundamentally fail to address systemic metastatic dissemination[3,4]. This dichotomy has perpetuated a false therapeutic binary—local versus systemic—that has constrained oncological practice for decades[5,6]. The urgent need to dismantle this barrier and forge genuinely integrative treatment paradigms has become increasingly apparent as cancer mortality from metastatic disease continues to dominate global cancer burden statistics[7].

1.2 The Abscopal Effect: From Biological Curiosity to Clinical Hope

he term "abscopal" (derived from Latin ab, away from, and scopus, target) was first coined by Mole in 1953[8] , though anecdotal reports of distant tumor regression following local radiation date back to the early 20th century [9]. For decades, this phenomenon remained a fascinating but clinically irrelevant biological curiosity, occurring too sporadically to warrant systematic investigation [10]. The contemporary renaissance of abscopal effect research began around 2012, catalyzed by the convergence of two transformative developments: the advent of stereotactic body radiotherapy (SBRT) capable of delivering ablative radiation doses with precision [11] , and the revolutionary success of immune checkpoint inhibitors (ICI) in unleashing antitumor immunity [12].

The modern operational definition of the abscopal effect encompasses any instance of tumor regression at non-treated distant sites following localized therapeutic intervention, including but not limited to radiotherapy, oncolytic virotherapy, and interventional ablation [13]. Its clinical significance transcends mere tumor shrinkage: it represents the first tangible demonstration that local therapy can be harnessed to achieve systemic disease control, thereby challenging the foundational premise that local and systemic treatments operate in mutually exclusive domains [14].

1.3 Current Bottlenecks

Despite mounting enthusiasm, three critical bottlenecks impede the clinical realization of abscopal effects:

Low incidence rates: In most solid tumor types, spontaneous or single-modality abscopal responses occur in fewer than 15% of patients, rendering them statistically and clinically negligible in routine practice[15, 16].

Unpredictability: The absence of reliable predictive biomarkers precludes patient selection, resulting in the application of expensive and potentially toxic combination regimens to broad populations with uncertain benefit[17, 18].

Mechanistic ambiguity: The optimal pairing of local "inducers" with systemic

"enhancers" remains empirically determined rather than rationally designed, reflecting incomplete understanding of the immunological choreography underlying successful abscopal responses[19, 20].

1.4 Core Thesis of This Review

We propose a dual-module strategic framework termed "Local Induction plus Systemic Enhancement" (LISE). Within this framework, Inducers comprise localized therapies that trigger the initial immunological spark through immunogenic cell death (ICD) and associated danger signal release [21, 22] . Enhancers encompass systemic therapeutic modalities that amplify, sustain, and systemically disseminate the immune response ignited by the inducer [23, 24] . This conceptual model moves beyond simple combination therapy toward a mechanistically grounded, sequence-dependent synergistic strategy. The central premise is that local therapy must first "light the fire" of antitumor immunity [25] , after which systemic agents function as "accelerants" that transform localized immune activation into a systemic conflagration capable of eradicating distant metastatic deposits [26,27]. The operational architecture of the LISE framework is depicted in Figure 1, illustrating the sequential dependency between local immune ignition and systemic response amplification.

Figure 1

The LISE Strategic Framework

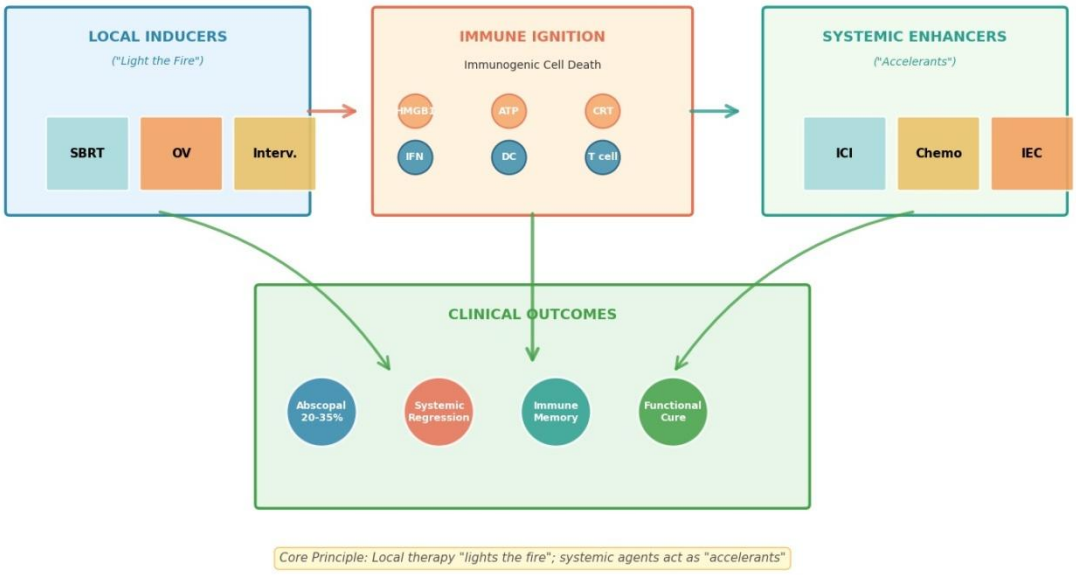

Figure 1. The "Local Induction plus Systemic Enhancement" (LISE) Strategic Framework. Local inducers (stereotactic body radiotherapy [SBRT], oncolytic viruses [OV], interventional therapies) trigger immunogenic cell death (ICD), releasing damage-associated molecular patterns (DAMPs: HMGB1, ATP, calreticulin [CRT]) and activating dendritic cells (DCs) and type I interferon (IFN) signaling. Systemic enhancers (immune checkpoint inhibitors [ICI], immune-modulating chemotherapy, immune effector cells [IEC] including CAR-T, CAR-NK, and TCR-T) function as "accelerants" that amplify localized immune activation into a systemic antitumor response. The framework emphasizes sequence-dependent synergy: local therapy must first "light the fire" of antitumor immunity, after which systemic agents transform localized

immune activation into systemic conflagration capable of eradicating distant metastatic deposits, achieving abscopal responses (20–35%), systemic tumor regression, immune memory formation, and functional cure potential.

2. The "Inducers": Local Therapies

The unifying mechanistic principle underlying all local inducers is the induction of immunogenic cell death (ICD), a regulated cell death modality characterized by the spatiotemporally coordinated emission of damage-associated molecular patterns (DAMPs) that alert and activate the innate immune system [28,29]. However, the three principal local therapeutic modalities—SBRT, oncolytic viruses, and interventional therapies—exhibit distinct immunological footprints, complementary strengths, and heterogeneous levels of clinical evidence[30-33].

2.1 Stereotactic Body Radiotherapy (SBRT)

2.1.1 Immunological Mechanisms

SBRT induces ICD through multiple convergent pathways. High-dose-per-fraction radiation (typically 6–20 Gy per fraction) triggers catastrophic DNA damage that activates the cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS-STING) pathway, a critical innate immune sensing mechanism that links cytosolic DNA recognition to type I interferon production [34, 35] . Concurrently, ICD is evidenced by the active release or surface exposure of canonical DAMPs including high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), and calreticulin (CRT) [36, 37] . These molecules serve as "find-me" and "eat-me" signals that recruit dendritic cells (DCs) and promote efficient antigen presentation to adaptive immune cells [36] .

A critical dose-immunology relationship has emerged from preclinical and translational studies: moderate hypofractionation (8–10 Gy × 3 fractions) appears optimal for immune activation, whereas single-fraction doses exceeding 12–18 Gy paradoxically activate the cytosolic exonuclease TREX1, which degrades cytosolic DNA and thereby attenuates cGAS-STING signaling [35,38,39]. This "immunological window" has profound implications for clinical protocol design, suggesting that maximal tumor cytotoxicity and maximal immunogenicity may not be congruent objectives [38]. The dose-immunology relationship and cGAS-STING activation cascade are illustrated in Figure 2A.

2.1.2 Clinical Evidence

The clinical evidence base for SBRT-induced abscopal effects has expanded substantially. In non-small cell lung cancer (NSCLC), the PEMBRO-RT phase II trial demonstrated that the addition of SBRT to pembrolizumab enhanced objective response rates from 18% to 36%, with abscopal responses observed in approximately one-third of treated patients [40]. In gastrointestinal (GI) malignancies, a 2026 meta-analysis encompassing 25 studies reported an aggregate abscopal effect rate of 26.2% and a 57% reduction in mortality risk among responders [41]. Notably, our institutional retrospective cohort of 68 patients with advanced gastrointestinal cancer treated between 2020–2025 who received first-line SBRT plus systemic therapy revealed an abscopal response rate of 27.9%, with three independent predictive factors identified: biologically effective dose (BED_{10}) $\geqslant$ 80Gy, first-line

immunotherapy administration, and microsatellite instability-high (MSI-H) status [42].

2.1.3 Limitations

The efficacy of SBRT as an inducer is constrained by several factors. Microsatellite stable (MSS) or immunologically "cold" tumors exhibit poor responses, reflecting inadequate baseline antigenicity and T cell infiltration [40,41]. Additionally, the physical limitations of radiation fields restrict applicability in patients with diffuse, multifocal metastatic disease where not all lesions can be encompassed within the treatment volume [43, 44].

2.2 Oncolytic Viruses (OV)

2.2.1 Immunological Mechanisms

Oncolytic viruses operate through a fundamentally distinct mechanism from radiation. Beyond direct viral oncolysis, they release viral-associated molecular patterns (VAMPs) that activate pattern recognition receptors including Toll-like receptors (TLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors[45,46]. A unique and critical distinction from SBRT is the introduction of viral neoantigens—foreign protein sequences absent from the host genome—that expand the immunological target repertoire beyond tumor-associated antigens [47,48] . Furthermore, recent evidence demonstrates that virus-infected cells release extracellular vesicles (EVs) containing viral components that can mediate remote transmission of immunological signals, potentially extending the inductive effect beyond the injected lesion [49,50] . The unique mechanisms of viral neoantigen introduction and EV-mediated signaling are depicted in Figure 2B.

2.2.2 Clinical Evidence

T-VEC (talimogene laherparepvec), a herpes simplex virus type 1 engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF), achieved FDA approval based on phase III melanoma data demonstrating durable response rates of 16.3% [51-53] . In GI malignancies, H101, a recombinant adenovirus, is currently under investigation in combination with SBRT and ICI for colorectal cancer liver metastases [54] . Newcastle disease virus (NDV) historical studies reported abscopal rates of 10–20%, though these data derive from methodologically heterogeneous early-phase trials [55, 56].

2.2.3 SBRT versus OV: Mechanistic Complementarity

The comparison between SBRT and OV reveals profound mechanistic complementarity rather than redundancy:

Dimension	SBRT	OV
Antigen source	Release of existing tumor antigens	Introduction of viral neoantigens
Immune action	Physical cytotoxicity	Biological infection plus immune stimulation
Action range	Dependent on immune cell trafficking	Viral particle dissemination via EVs
Optimal population	MSI-H, immunologically "hot" tumors	MSS, "cold" tumors, ICI-resistant disease

This complementarity suggests that strategic sequencing or combination of SBRT and OV may achieve synergistic inductive capacity exceeding either modality alone.

2.3 Interventional Therapies

2.3.1 Technical Spectrum

Interventional inducers encompass transarterial chemoembolization (TACE), thermal ablation (radiofrequency, microwave, cryoablation), hepatic arterial infusion chemotherapy (HAIC), and irreversible electroporation (IRE)[57-61].

2.3.2 Immunological Mechanisms

Ischemia and hyperthermia induced by TACE and thermal ablation trigger necroptotic cell death, an ICD variant characterized by mixed lineage kinase domain-like protein (MLKL)-mediated plasma membrane rupture and robust DAMP release [60,62]. Cryoablation uniquely preserves antigenic integrity through freezing rather than denaturation, potentially yielding superior immunogenicity[63,64]. IRE, which creates nanopores in cell membranes through pulsed electrical fields, has demonstrated particularly high immunogenic potential in preclinical models [61, 65]. The diverse cell death modalities induced by interventional therapies are summarized in Figure 2C.

2.3.3 Clinical Evidence

The clinical evidence for interventional therapies as abscopal inducers remains comparatively limited. TACE combined with ICI in hepatocellular carcinoma retrospective studies reported abscopal rates of 7.1% [66,67] . Cryoablation has been associated with abscopal responses in prostate and renal cell carcinoma case reports [68-70] . Overall, the evidence grade is low, dominated by small-sample retrospective series and lacking prospective validation [71,72] .

2.4 Chapter Summary

Table 1. Comparison of Three "Inducer" Modalities

Strategy	Core Mechanism	Evidence Grade	Single-Agent Abscopal Rate	Major Limitation
SBRT	ICD, DAMPs, cGAS-STING	High	5–10%	Poor response in MSS tumors
Oncolytic virus	Viral oncolysis + VAMPs + eoantigens	Moderate-High	5–12%	Technical demands of intratumoral injection
Interventional therapy	Ischemia/hyperthermia-induced antigen release	Low	<5%	Absence of prospective studies

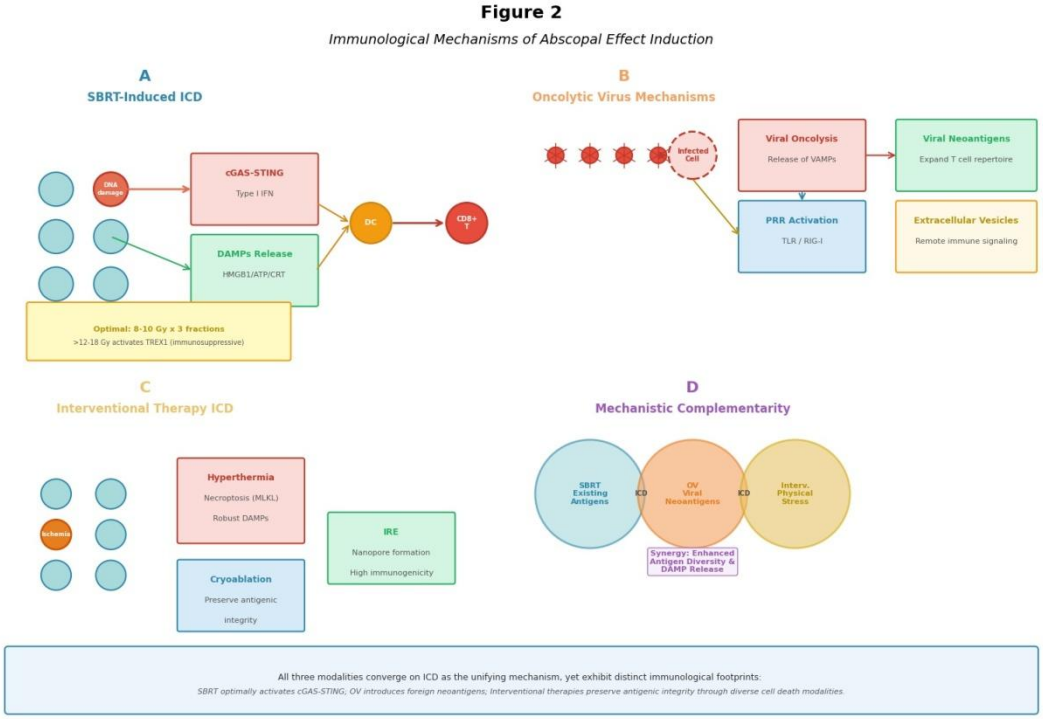

Figure 2. Immunological Mechanisms of Abscopal Effect Induction (A) SBRT-induced immunogenic cell death (ICD) activates the cGAS-STING pathway and releases canonical DAMPs (HMGB1, ATP, CRT), promoting dendritic cell (DC) maturation and CD8+ T cell priming. The optimal immunological window (8–10 Gy × 3 fractions) is highlighted, with higher single-fraction doses paradoxically activating TREX1-mediated immunosuppression. (B) Oncolytic viruses mediate immunogenic cell death through viral oncolysis, pattern recognition receptor (PRR) activation (TLR/RIG-I), introduction of viral neoantigens, and extracellular vesicle (EV)-mediated remote immune signaling. (C) Interventional therapies (TACE, thermal ablation, cryoablation, IRE) induce diverse ICD modalities including necroptosis (MLKL-mediated) and preserve antigenic integrity. (D) Mechanistic complementarity among the three modalities: SBRT releases existing tumor antigens, OV introduces foreign viral neoantigens, and interventional therapies provide physical stress-induced antigen release, collectively enhancing antigenic diversity.

3. The "Enhancers": Systemic Therapies

The unifying principle of systemic enhancers is that they cannot independently induce abscopal effects but function to dismantle immunosuppressive barriers, deliver effector cells, and remodel the tumor microenvironment (TME), thereby amplifying the localized immune ignition initiated by inducers into a systemic antitumor immune response[73,74].

3.1 Immune Checkpoint Inhibitors (ICI) — The Best-Evidence "Accelerant"

3.1.1 Mechanisms

ICIs function by blocking inhibitory immune checkpoint axes—principally programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)—that tumors exploit to evade immune surveillance [75,76]. By "releasing the brakes" on T cell activation, ICIs

enhance $CD8^+$ cytotoxic T lymphocyte proliferation, survival, and effector function [77, 78]. Their role within the LISE framework is conceptually distinct from their use as monotherapy: rather than relying on endogenous antitumor immunity that is often exhausted or absent, ICI-enhanced regimens capitalize on the fresh immune activation generated by local inducers [79,80].

3.1.2 Clinical Evidence

The combination of SBRT with ICI represents the most extensively validated abscopal strategy, with abscopal rates of 20–35% across multiple tumor types—representing a three- to four-fold increase over radiation monotherapy [41, 81, 82]. The 2026 GI cancer meta-analysis confirmed a 57% mortality risk reduction among patients achieving abscopal responses [41]. Our institutional data further support these findings: first-line ICI plus SBRT conferred an odds ratio (OR) of 3.78 for abscopal response, while MSI-H status conferred an OR of 5.10, underscoring the critical importance of both treatment timing and tumor immunogenicity [42]. The quantitative efficacy comparison across strategies is presented in Figure 3A, and the predictive factor analysis is detailed in Figure 3B.

3.1.3 Limitations

ICI enhancement is fundamentally constrained by the quality of the underlying immune response. In MSS or immunologically "cold" tumors with minimal baseline T cell infiltration, ICIs are ineffective as monotherapy and demonstrate diminished capacity to enhance locally induced immunity [83, 84] . Furthermore, ICI efficacy remains contingent upon local therapy successfully "igniting" the initial immune response—a prerequisite that is not universally met [85, 86].

3.2 Immune-Modulating Chemotherapy and Anti-Angiogenesis — The Mid-Tier "Accelerants"

3.2.1 Immune-Modulating Chemotherapy

Metronomic chemotherapy—characterized by low-dose, continuous administration rather than maximum tolerated dose boluses—exerts immunomodulatory effects distinct from its cytotoxic actions. Cyclophosphamide at metronomic doses selectively depletes regulatory T cells (Tregs) [87, 88], while oxaliplatin induces immunogenic cell death [89]. These agents function as enhancers primarily in the context of established local immune activation, though standalone abscopal induction is exceedingly rare [90].

3.2.2 Anti-Angiogenic Therapy

Vascular endothelial growth factor (VEGF) inhibitors, including bevacizumab and lenvatinib, promote TME normalization by pruning aberrant tumor vasculature and reducing hypoxia, thereby facilitating T cell infiltration and improving drug delivery [91, 92] . Our institutional data demonstrated that the addition of anti-angiogenic therapy to immunotherapy increased abscopal rates from 13.6% to 35.3% ($P = 0.027$), establishing this combination as a clinically meaningful enhancement strategy, particularly in hypervascular tumors such as hepatocellular carcinoma [42].

3.3 Immune Effector Cell Therapy (CAR-T/CAR-NK/TCR-T) — The Emerging ‘Super-Accelerants’

This section represents the core innovative contribution of this review, positioning

CAR-T, CAR-NK and TCR-T cell therapies not merely as standalone treatments but as the next-generation enhancers within the LISE framework.

3.3.1 Why the "Strongest Accelerant"?

The conceptual distinction between ICI and CAR-T as enhancers is profound and operationally critical [93, 94]:

Dimension	ICI	CAR-T
Core action	Disinhibition of existing T cells ("releasing brakes")	De novo delivery of engineered killer cells ("installing new engine")
Cold tumor efficacy	Limited	Potentially transformative after local empowerment
Persistence	Dependent on endogenous immune memory	CAR-T cells can expand and persist autonomously
Endogenous T cell dependence	High	Can operate independently of host immunity

CAR-T cells represent a fundamentally different category of enhancer: rather than attempting to salvage exhausted endogenous immunity, they introduce a fully competent, tumor-targeted cellular therapeutic that can be "empowered" by local inducers to overcome the unique barriers of solid tumor immunotherapy[95, 96]. The multi-dimensional comparative assessment of enhancer modalities is illustrated in Figure 3D, highlighting the complementary strengths of ICI and CAR-T-based strategies.

3.3.2 How Local Therapy "Empowers" CAR-T

Table 2. Local Therapy Mechanisms of CAR-T Empowerment

Local Therapy	Empowerment Mechanism	Key Evidence	Publication
SBRT	Upregulation of target antigen expression; promotion of T cell infiltration; TME remodeling	Proton RT + mesothelin-directed CAR-T: systemic tumor regression	NIH, 2024
Oncolytic virus	Chemokine-mediated CAR-T recruitment; conversion of cold to hot tumors	rNDV19 + CAR-T: significant survival prolongation	JITC, 2025
Microwave ablation	Macrophage activation; creation of immune "beacon signals"	sCAR-T + MWA: macrophage-mediated abscopal effects	Cell Reports Medicine, 2025

The convergence of local inducers with CAR-T therapy addresses the three cardinal barriers to solid tumor CAR-T efficacy: antigen heterogeneity (through local upregulation of target expression), physical exclusion (through TME remodeling and chemokine recruitment), and functional exhaustion (through provision of activating innate immune signals) [97, 98].

3.3.3 Overcoming Antigen Heterogeneity: From "Precision Strike" to "Domain Clearance"

A persistent limitation of conventional CAR-T therapy is antigen heterogeneity—tumor subclones lacking the target antigen escape CAR-T-mediated killing, leading to inevitable relapse[99,100]. The novel paradigm exemplified by sCAR-T (switchable CAR-T) combined with microwave ablation offers a revolutionary solution: by recruiting and reprogramming tumor-associated macrophages (TAMs) through locally released cytokine and chemokine signals, this

strategy achieves antigen-independent abscopal clearance of distant lesions[101, 102]. The macrophage-mediated bystander killing effect circumvents the fundamental constraint of antigen homogeneity, offering a viable strategy for MSS-type tumors with antigen loss variants.

3.3.4 Clinical Translation Status

While CAR-T therapy has achieved remarkable success in hematological malignancies (CD19, BCMA targets), solid tumor application remains limited by infiltration barriers[103, 104]. The integration of local inducers represents the most promising strategy to overcome this bottleneck. Active clinical trials include NCT04370418 (oncolytic virus plus CAR-T) and NCT03635632 (TCR-T plus radiotherapy), with initial safety and efficacy data anticipated within the next 24–36 months[105, 106].

3.3.5 CAR-NK: The Innate "Super-Accelerant"

CAR-NK cells represent a compelling alternative to CAR-T within the LISE framework, offering distinct advantages: MHC-independent tumor recognition, absence of CRS/GVHD risk, and "off-the-shelf" manufacturability [107, 108]. Preclinical evidence directly supports the abscopal potential of local CAR-NK therapy: in a bilateral glioblastoma mouse model, local injection of HER2-specific CAR-NK cells combined with systemic anti-PD-1 induced regression of both treated and contralateral untreated tumors, demonstrating a true abscopal effect [109]. Furthermore, radiotherapy has been shown to enhance CAR-NK tumor infiltration and therapeutic efficacy in rhabdomyosarcoma models [110]. These findings position CAR-NK as a promising next-generation enhancer that, when empowered by local inducers, could overcome the infiltration and persistence barriers that currently limit solid tumor cell therapy. Active clinical trials include NCT04623944 (NKX101 in AML/MDS) and NCT07589543 (dual-target CAR-NK in ovarian cancer) [111, 112].

3.4 Chapter Summary

Table 3. Comparison of "Enhancer" Modalities

Enhancer Type	Core Mechanism	Dependence on Local Therapy	Evidence Grade	Unique Value
ICI	T cell disinhibition ("releasing brakes")	Moderate-High	High	Universal applicability; strongest evidence base
Immune-modulating chemotherapy	Treg/MDSC depletion	High	Low-Moderate	Applicable in widely metastatic disease
Anti-angiogenic therapy	Ischemia/hyperthermia-induced antigen release	Moderate	Moderate	Synergistic with ICI
CAR-T/CAR-NK/TCR-T	De novo cellular therapy + macrophage recruitment ("installing new engine")	High	Low-Moderate (preclinical to early clinical)	Greatest "zero-to-one" potential; independent of endogenous immunity

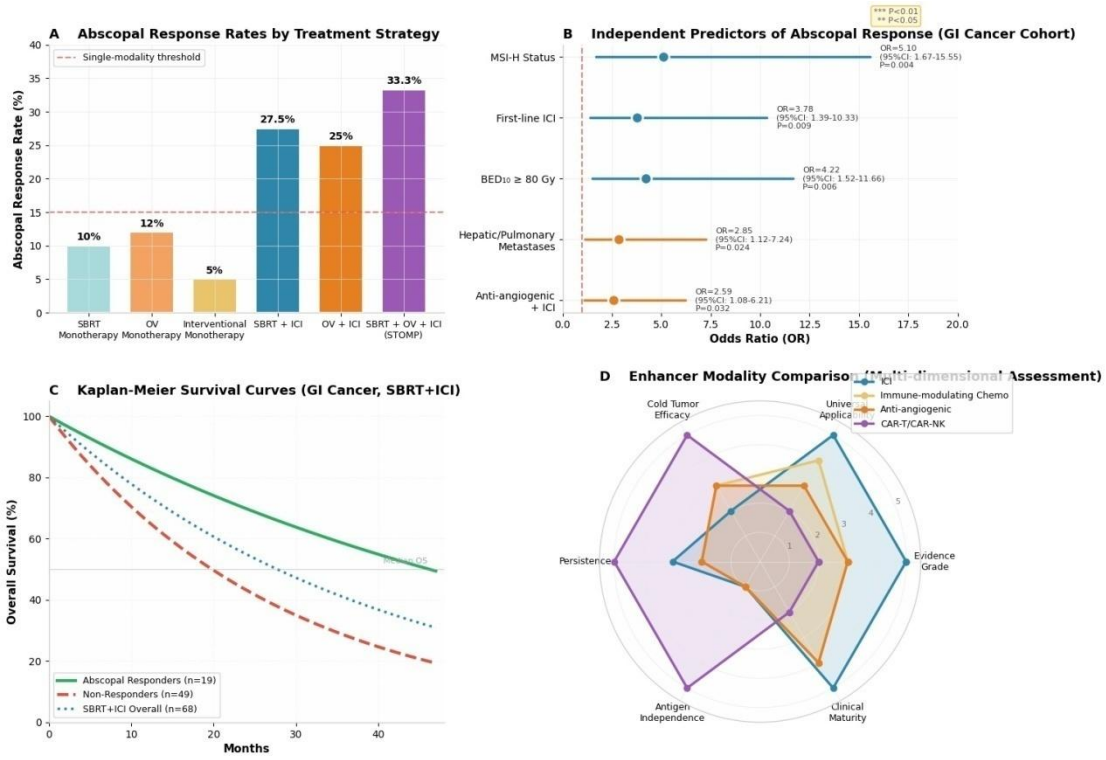

Figure 3. Clinical Evidence and Efficacy Assessment of Abscopal Effect-Based Strategies (A) Abscopal response rates across treatment strategies. Single-modality therapies (SBRT, OV, interventional) achieve <15% abscopal rates, whereas combination strategies (SBRT+ICI, OV+ICI) demonstrate 20–35% rates, with the STOMP trial triplet (SBRT+OV+ICI) reaching 33.3%. (B) Forest plot of independent predictors of abscopal response in gastrointestinal cancer (institutional cohort, n=68). MSI-H status confers the highest odds ratio (OR=5.10), followed by BED_{10} ≥80 Gy (OR=4.22) and first-line immunotherapy (OR=3.78). (C) Kaplan-Meier survival curves demonstrating superior overall survival in abscopal responders versus non-responders following SBRT+ICI treatment. (D) Radar plot multi-dimensional comparison of enhancer modalities: ICI demonstrates the highest evidence grade and universal applicability; CAR-T/CAR-NK exhibits superior cold tumor efficacy, persistence, and antigen independence but lower clinical maturity.

4. Strategy Integration: From "Solo Combat" to "Synergistic Warfare"

The central thesis of the LISE framework is that inducer-enhancer pairing must be rationally matched to tumor biology and clinical context rather than applied empirically.

4.1 The Best-Evidence "Golden Combination": SBRT + ICI

4.1.1 Efficacy Data

The SBRT-ICI combination yields abscopal rates of 20–35% across pooled analyses, with the 2026 GI cancer meta-analysis reporting 26.2% and a 57% mortality risk reduction[41]. These figures represent a clinically meaningful and statistically robust improvement over any single-modality approach.

4.1.2 Predictive Factors: Three Independent Determinants

Our institutional analysis identified three independent predictors of abscopal response in GI cancer[42]:

Predictor	Odds Ratio	95% Confidence Interval	P-value
BED_{10}⩾80 Gy	4.215	1.523–11.657	0.006

First-line immunotherapy	3.782	1.386–10.325	0.009
MSI-H status	5.103	1.674–15.552	0.004

The three independent predictive determinants identified in our institutional analysis are visualized in Figure 3B with corresponding odds ratios and confidence intervals.

4.1.3 Optimization Strategies

Radiation dosing: $BED_{10} \geq 80$ Gy (e.g., 50 Gy in 5 fractions) appears to represent an immunological threshold above which abscopal probability increases substantially[113, 114].

Treatment timing: First-line administration (OR = 3.78 versus later lines) suggests that immune system integrity and tumor antigen burden are maximal early in the disease course[42].

Patient selection: MSI-H status confers the highest predictive value (OR = 5.10), while hepatic and pulmonary metastases demonstrate favorable abscopal rates (37.1%), potentially reflecting organ-specific immune microenvironment characteristics[42, 115].

4.2 Promising "Innovative Combinations"

4.2.1 Oncolytic Virus + ICI

The STOMP trial in NSCLC demonstrated that the triplet of oncolytic virus, SBRT, and ICI achieved an objective response rate of 33.3%, with 75% of ICI-resistant patients deriving clinical benefit[116]. This finding is of exceptional significance: it establishes OV as a strategy capable of resensitizing ICI-resistant tumors, potentially by introducing viral neoantigens that reactivate exhausted or ignorant T cell clones[117].

4.2.2 SBRT + Oncolytic Virus (± ICI)

The mechanistic complementarity between SBRT (existing antigen release) and OV (viral neoantigen introduction) provides a rational basis for dual-inducer strategies[117, 44]. Theoretical modeling suggests that triplet regimens (SBRT + OV + ICI) could achieve abscopal rates of 40–50%, though this remains to be prospectively validated. The ongoing H101 + SBRT + ICI trial for CRC liver metastases (ChiCTR2200055027) represents a critical test of this hypothesis.

4.2.3 SBRT/OV + CAR-T

Preclinical evidence for local therapy-CAR-T combinations is robust and mechanistically compelling (see Section 3.3.2). Clinical translation is in early-phase trials, but the strategic value is potentially transformative: this combination may represent a potential strategy for overcoming MSS-type, ICI-resistant, and antigen-heterogeneous tumors that are refractory to all current standard approaches[23, 31].

4.3 Highly Individualized Clinical Decision Pathways

4.3.1 Decision Variables

Variable	Recommended Strategy
MSI-H / TMB-H	SBRT + ICI (first-line; expected abscopal rate ~50%)
MSS / Cold tumor	(1) Oncolytic virus + ICI; (2) Triplet (SBRT + OV + ICI)
ICI-resistant	Oncolytic virus ± SBRT (STOMP: 75% benefit rate) or CAR-T combination
Antigen heterogeneity/loss	Microwave ablation + sCAR-T (macrophage-mediated)
Hepatic/pulmonary oligometastases	SBRT + ICI (hepatic metastases: 37.1% abscopal rate)

Peritoneal metastases	Poorest abscopal rates (8.3%); consider CAR-T or intraperitoneal therapy
First-line treatment	SBRT + ICI (superior to later lines; OR = 3.78)

The clinical decision algorithm is presented in Figure 4, providing a structured flowchart for treatment selection based on tumor biology and clinical context.

4.3.2 Decision Algorithm

The clinical implementation of the LISE framework requires a structured decision algorithm. The optimal treatment sequencing timeline, from local induction through abscopal response assessment, is depicted in the lower panel of Figure 4.

Figure 4

Clinical Decision Algorithm for LISE Framework Implementation

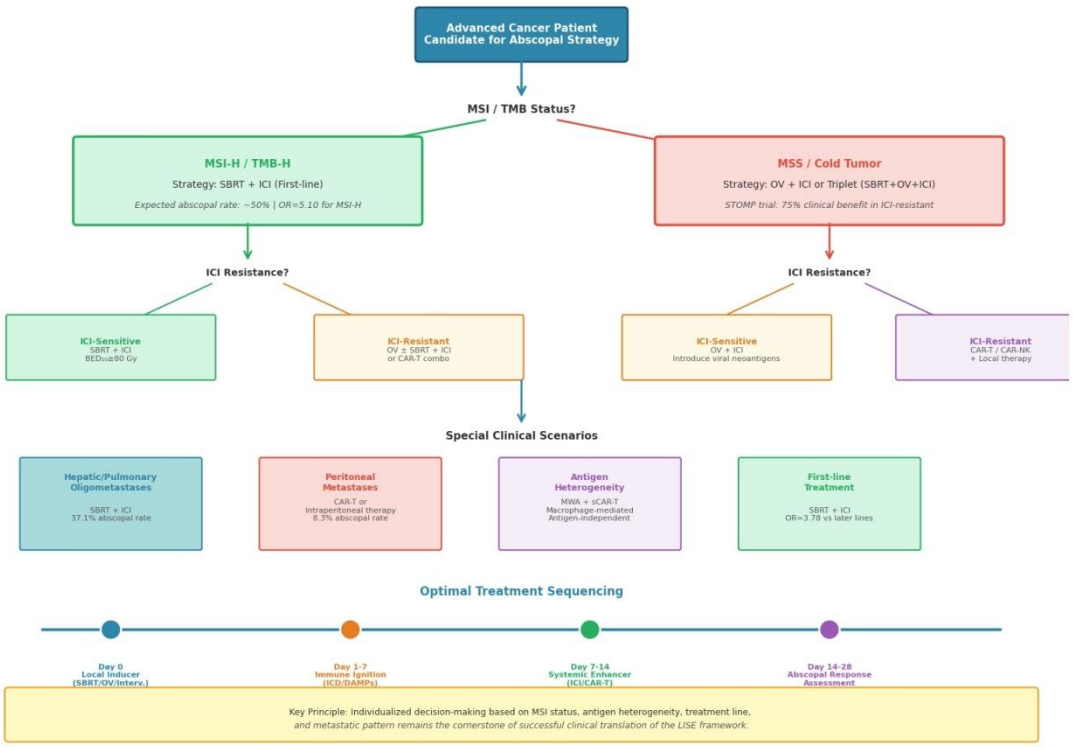

Figure 4. Clinical Decision Algorithm for LISE Framework Implementation. Structured decision tree for individualized abscopal effect-based therapy selection. The algorithm stratifies patients by MSI/TMB status (MSI-H vs. MSS/cold tumor), ICI resistance profile, metastatic pattern (hepatic/pulmonary vs. peritoneal), antigen heterogeneity, and treatment line. Optimal treatment sequencing is proposed: Day 0 (local inducer), Day 1–7 (immune ignition/ICD), Day 7–14 (systemic enhancer), Day 14–28 (abscopal response assessment). MSI-H patients receive SBRT+ICI first-line (expected abscopal rate ~50%); MSS/cold tumors are directed to OV+ICI or triplet strategies; ICI-resistant cases are candidates for CAR-T/CAR-NK combinations; antigen-heterogeneous tumors are treated with microwave ablation + sCAR-T (macrophage-mediated clearance).

5. Challenges and Future Directions

5.1 Current Challenges

Low evidence grade: The abscopal effect literature remains dominated by retrospective analyses, small single-institution series, and case reports. Prospective randomized controlled trials (RCTs) with abscopal response as a primary or secondary endpoint are critically needed but remain scarce[118].

Biomarker deficiency: No validated biomarker currently predicts abscopal response probability. Candidate markers—including peripheral T cell receptor (TCR) clonality, circulating tumor DNA (ctDNA) dynamics, and systemic cytokine profiles—require prospective validation[119, 120].

Standardization deficit: Optimal radiation dose-fractionation, oncolytic viral dosing, and treatment sequencing (inducer before enhancer, concurrent, or sequenced) remain undefined, reflecting the early stage of clinical development.

Safety management: The combination of potent immune activators (radiation, viruses, ICI, CAR-T/ CAR-NK) introduces novel toxicity profiles including overlapping risks of pneumonitis, cytokine release syndrome, and neurotoxicity that require systematic characterization.

5.2 Future Directions

5.2.1 Novel "Inducers"

FLASH radiotherapy: Ultra-high dose-rate radiation (≥40 Gy/s) spares normal tissue while maintaining tumor cytotoxicity, with preliminary evidence suggesting enhanced immune sparing that may improve the therapeutic index for abscopal induction[121, 122, 118].

Multi-target SBRT: Simultaneous irradiation of 2–4 metastatic lesions may increase antigenic diversity and broaden the T cell response, potentially overcoming clonal antigen loss—a strategy currently under investigation in the I-SPY platform trial.

5.2.2 Novel "Enhancers"

Armed oncolytic viruses: Next-generation OVs engineered to express bispecific T cell engagers (BiTEs), interleukin-12 (IL-12), or anti-PD-1 antibodies directly within the TME represent "self-enhancing inducers" that blur the inducer-enhancer boundary[123, 124].

STING agonists: Systemic administration of cGAS-STING pathway activators (ADU-S100, MK-1454) may pharmacologically replicate the immunological effects of radiation, currently in phase I development[120].

5.2.3 Targeting Microenvironmental Barriers

The landmark study by Wu et al. (2025, Cancer Cell) identified plasminogen activator inhibitor-1 (PAI-1) and secreted frizzled-related protein 2 (SFRP2) as critical mediators of cancer-associated fibroblast (CAF)-mediated immune exclusion. Inhibition of these axes restores T cell infiltration and may be essential for converting CAF-barricaded tumors into abscopal-responsive phenotypes[125]. The PAI-1/SFRP2 axis-mediated immune exclusion mechanism, recently identified by Zhang et al[125]. (2025, Cancer Cell), is illustrated in Figure 5C. Irradiated tumor-secreted PAI-1 drives pericyte lineage commitment to SFRP2high CAFs via the LRP1/p65 axis, creating a hostile perivascular niche that excludes CD8+ T cells from distant tumors. Pharmacological inhibition of this axis represents a promising strategy to convert CAF-barricaded tumors into abscopal-responsive phenotypes. As noted in a concurrent commentary, targeting PAI-1 or SFRP2 enhances T cell recruitment and prevents the formation of an immunosuppressive perivascular niche [126].

5.2.4 Biomarker Development

Peripheral blood: TCR clonal expansion dynamics, ctDNA clearance kinetics, and

multiplex cytokine profiling offer non-invasive monitoring tools[119, 120].

Tissue biomarkers: PAI-1/SFRP2 expression, CAF subtype composition, and composite TME immune scores may enable pretreatment stratification[125]. Candidate biomarkers for prospective validation are categorized in Figure 5D into peripheral blood-based and tissue-based approaches.

Figure 5

Future Directions: Overcoming Microenvironmental Barriers to Abscopal Effects

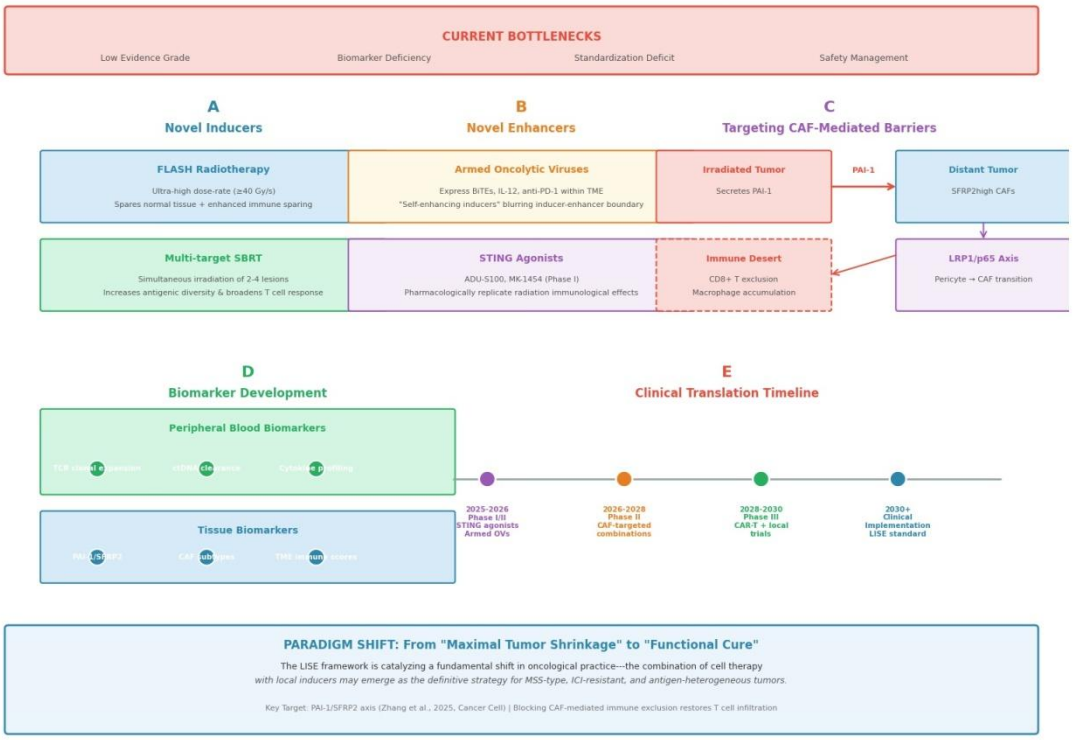

Figure 5. Future Directions: Overcoming Microenvironmental Barriers to Abscopal Effects (A) Novel inducers: FLASH radiotherapy (≥40 Gy/s) spares normal tissue while maintaining immunogenicity; multi-target SBRT increases antigenic diversity. (B) Novel enhancers: Armed oncolytic viruses expressing BiTEs, IL-12, or anti-PD-1 within the TME; STING agonists (ADU-S100, MK-1454) pharmacologically replicate radiation-induced immune activation. (C) Targeting CAF-mediated barriers: The PAI-1/SFRP2 axis represents a critical stromal regulator of abscopal response. Irradiated tumors secrete PAI-1, which triggers distant tumor pericyte-to-CAF transition via the LRP1/p65 axis, creating an immune desert (CD8+ T exclusion, macrophage accumulation). Pharmacological blockade of PAI-1 or SFRP2 restores T cell infiltration. (D) Biomarker development: Peripheral blood (TCR clonality, ctDNA, cytokines) and tissue (PAI-1/SFRP2, CAF subtypes, TME scores) biomarkers for pretreatment stratification. (E) Clinical translation timeline: Phase I/II (2025–2026) for STING agonists and armed OVs; Phase II (2026–2028) for CAF-targeted combinations; Phase III (2028–2030) for CAR-T+local therapy trials; clinical implementation (2030+) of LISE as standard of care.

6. Conclusion

The "Local Induction plus Systemic Enhancement" framework represents the optimal current strategy for achieving clinically meaningful abscopal effects in advanced cancer[15,127]. Within this paradigm, inducer selection should be guided by evidence grade (SBRT strongest), mechanism (OV complementary for cold tumors), and

technical accessibility (interventional therapies for specialized scenarios). Enhancer matching should prioritize ICI as the most universally applicable accelerant, while positioning CAR-T/CAR-NK/TCR-T therapies as the most transformative future direction[128, 129].

The core operational principle can be distilled to a simple but profound maxim: local therapy must first "light the fire," after which systemic agents function as "accelerants" or "new engines." Successful clinical implementation demands three elements: selection of the appropriate "ignition source" (SBRT versus OV versus interventional therapy), matching with the optimal "accelerant" (ICI versus CAR-T/CAR-NK/TCR-T versus chemotherapy/anti-angiogenesis), and precise timing (first-line, oligometastatic disease).

Looking forward, the strategic targeting of microenvironmental barriers—particularly the PAI-1/SFRP2 axis (Figure 5C)—combined with next-generation inducers and enhancers (Figure 5A-B), positions the LISE framework to achieve the aspirational goal of functional cure through systemic immune-mediated disease control (Figure 5E).

Looking forward, this strategic framework is catalyzing a fundamental paradigm shift in oncological practice—from the traditional objective of "maximal tumor shrinkage" toward the aspirational goal of "functional cure" through systemic immune-mediated disease control. The combination of cell therapy with local inducers, in particular, may emerge as the definitive therapeutic strategy for MSS-type, ICI-resistant, and antigen-heterogeneous tumors that currently defy all standard approaches[129-131]. The abscopal effect, once a biological curiosity, is poised to become the cornerstone of integrative cancer immunotherapy in the decade ahead[127, 132].

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