Stereotactic Radiosurgery and Immunotherapy for Melanoma and NSCLC Brain Metastases: Practical Integration, Timing, and Toxicity

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Abstract

Brain metastases remain a major cause of morbidity and mortality in patients with cancer, particularly melanoma and non-small cell lung cancer. Stereotactic radiosurgery (SRS) is a cornerstone of management for limited intracranial disease, offering high local control while minimizing the neurocognitive toxicity associated with whole-brain radiation therapy. Immune checkpoint inhibitors (ICIs) have also transformed systemic therapy for tumors with central nervous system involvement, creating an increasing clinical need to define how best to integrate these modalities. The combined use of SRS and ICIs has raised an important question regarding optimal treatment timing. Retrospective evidence suggests that concurrent or near-concurrent administration, commonly defined as treatment within approximately 2-4 weeks, may improve local control and intracranial response. Several studies also suggest a potential survival advantage compared with sequential treatment, although these findings are limited by selection bias and require prospective validation. Most contemporary analyses do not show a significant increase in radionecrosis with concurrent single-agent ICI; however, emerging data suggest that dual checkpoint blockade may increase the risk of symptomatic radionecrosis. This narrative review synthesizes the biologic rationale, clinical evidence, and toxicity considerations for combining SRS and ICIs in patients with brain metastases. We emphasize differences between single-agent and dual ICI strategies, highlight dosimetric predictors of radionecrosis such as V12 Gy, and propose a practical framework for treatment integration. Overall, concurrent SRS with single-agent ICI appears feasible and is associated with favorable intracranial outcomes in selected patients, whereas dual ICI warrants more cautious, individualized decision-making. Prospective studies are needed to define optimal sequencing, patient selection, and toxicity mitigation strategies.

Keywords: stereotactic radiosurgery, immunotherapy, brain metastases, immune checkpoint inhibitors, melanoma, non-small cell lung cancer, radionecrosis, treatment timing, V12 Gy, hypofractionation

Introduction

Brain metastases occur in up to 20%-40% of patients with advanced solid malignancies and remain a major cause of neurologic morbidity and mortality.[1] The incidence is particularly high in melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC), reflecting tumor biology and improved systemic therapies that prolong survival.[2] Although breast cancer is also a common source, it is not emphasized here due to the evolving role of immune checkpoint inhibitors (ICIs) in this setting.[3,4] Over the past decade, management has shifted toward focal therapies such as stereotactic radiosurgery (SRS) rather than

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whole-brain radiation therapy (WBRT) in appropriately selected patients.[5]

SRS is a standard treatment for brain metastases, delivering highly conformal ablative doses with excellent local control while preserving neurocognitive function.[6] Recent randomized data suggest that, in selected patients with multiple brain metastases, SRS may provide superior cognitive outcomes compared with hippocampal avoidance WBRT.[7] Concurrently, ICIs have transformed systemic therapy for melanoma, NSCLC, and other malignancies with central nervous system involvement.[8] As a result, patients increasingly receive both SRS and ICIs during their treatment course.[9]

This convergence raises a key clinical question: how should SRS and ICIs be optimally integrated, and does treatment timing influence outcomes and toxicity? The rationale for combination is biologically compelling. Radiation enhances tumor immunogenicity through antigen release, dendritic cell activation, and T-cell priming, potentially synergizing with checkpoint blockade.[10] However, this immune activation may also increase inflammatory toxicity, including radiation necrosis (RN) and edema.[11]

Despite expanding clinical experience, optimal sequencing remains uncertain. Current evidence is largely retrospective and heterogeneous, with variable definitions of "concurrent" therapy and differences in histology and treatment regimens. Nonetheless, consistent patterns suggest improved intracranial outcomes with concurrent treatment and highlight important toxicity differences between single-agent and dual ICI strategies.[12,13]

This narrative review provides a clinically focused synthesis of the evidence on SRS-ICI integration in brain metastases, emphasizing biologic rationale, treatment timing, efficacy, and toxicity. We also propose a practical framework for clinical decision-making and highlight key areas for future research.

Methods of Literature Review

This narrative review was conducted using focused searches of PubMed, Embase, and Scopus. Search terms included combinations of "brain metastases," "stereotactic radiosurgery," "stereotactic radiation therapy," "immune checkpoint inhibitors," "PD-1," "PD-L1," "CTLA-4," "timing," "concurrent," "sequential," and "radionecrosis."

Priority was given to multicenter studies, contemporary retrospective analyses, prospective trials, and meta-analyses published between 2016 and 2026. Studies evaluating treatment timing, local control, overall survival, and RN were included, with emphasis on melanoma and NSCLC cohorts.

Biological Rationale for Combining SRS and Immunotherapy

The rationale for combining SRS with ICIs is based on radiation-induced immune modulation.[10] High-dose focal radiation promotes immunogenic cell death, enhancing antigen release, dendritic cell activation, and T-cell priming, thereby transforming the irradiated lesion into an in situ vaccine-like stimulus.[14,15]

Radiation also modulates the tumor microenvironment by increasing major histocompatibility complex expression, enhancing T-cell infiltration, and altering cytokine signaling.[16] These effects may augment ICI efficacy, which functions by relieving inhibitory signals on T cells and sustaining antitumor immune responses.[17] This biologic synergy supports combining SRS and ICIs, particularly when delivered in close temporal proximity.[18-20]

However, these same mechanisms may also increase toxicity. RN is a multifactorial process involving vascular injury, hypoxia, and immune-mediated inflammation.[21] ICIs may amplify these pathways, particularly with dual checkpoint blockade, potentially increasing the risk of treatment-related toxicity.[11]

Clinical Evidence on Treatment Timing

Definition of Concurrent Treatment

A major limitation in the literature is the lack of a standardized definition of "concurrent" treatment. Definitions vary across studies, ranging from within 1, 2, or 4 weeks to within one pharmacokinetic half-life of the ICI agent.[19]

Despite this variability, most studies adopt a practical definition of concurrent therapy as SRS delivered within approximately 2 to 4 weeks of ICI administration.[9,13] Some analyses suggest that shorter intervals, particularly within 2 weeks or one half-life, may be associated with improved intracranial response, although optimal timing remains uncertain.[19]

Evidence in Melanoma

The emergence of dual checkpoint blockade has significantly altered the management of melanoma brain metastases.[22] Prospective phase II studies have demonstrated durable intracranial activity with nivolumab plus ipilimumab in asymptomatic patients. In CheckMate 204, Tawbi et al reported an intracranial objective response rate of 57%, establishing dual checkpoint blockade as a highly active systemic therapy for untreated melanoma brain metastases.[23] Long-term follow-up demonstrated durable benefit, with 3-year intracranial progression-free survival and overall survival rates of 54.1% and 71.9%, respectively.[24] Similarly, the randomized phase II ABC trial showed superior intracranial response and long-term survival with

nivolumab plus ipilimumab compared with nivolumab alone, supporting dual checkpoint blockade as the preferred systemic approach in asymptomatic patients.[25] These findings have raised important questions regarding the optimal integration of SRS, which are being addressed in the ongoing ABC-X trial evaluating nivolumab plus ipilimumab with or without concurrent intracranial SRS.[26]

Against this backdrop of highly effective systemic therapy, multiple retrospective studies have evaluated whether the addition and timing of SRS further improve intracranial outcomes. Kotecha et al reported that timing influences efficacy more than toxicity, with concurrent ICI improving response and low RN (3%-5%),[19] while Carron et al confirmed low toxicity with anti-PD-1 therapy (adverse radiation effect 4%-5%, symptomatic <3%).[27]

Regimens incorporating CTLA-4 inhibition, particularly dual ICI, are associated with higher RN rates, although estimates vary. Minniti et al reported moderate RN (15%-25%) with concurrent nivolumab/ipilimumab.[28] In contrast, Tang et al demonstrated significantly improved local control (92% vs 64%) without excess toxicity or increased RN.[29] Fu et al similarly observed improved survival with concurrent SRS-ICI (37.1 vs 11.4 months) without increased radiation toxicity (2%-3%).[30] More recent data from Messing et al show excellent local control (90%) with low symptomatic RN (7%), while identifying prior systemic therapy as a prognostic factor.[31] Conversely, Vaios et al reported higher RN rates with dual ICI (20%-25%),[11] whereas Mandalà et al demonstrated survival benefit with moderate RN (10%).[32] Key retrospective studies are summarized in **Table 1**.

Overall, evidence is heterogeneous and predominantly retrospective yet supports close temporal integration of SRS and ICI to optimize intracranial control. ICI regimen and prior therapy exposure may influence toxicity and outcomes, warranting prospective validation.

Evidence in NSCLC

NSCLC has a growing but less mature evidence base for SRS-ICI integration compared with melanoma. Early-phase prospective studies demonstrate feasibility, safety, and encouraging intracranial control.[33-36]

Across retrospective cohorts, SRS combined with ICI has consistently been associated with improved intracranial control and, in some studies, overall survival. Foundational studies by Chen et al and Schapira et al demonstrated superior survival and intracranial control with concurrent SRS-ICI (within 2-4 wk) compared with nonconcurrent approaches.[13,37] Larger analyses, including Yomo et al, confirmed improved survival (mOS 16.9 vs 12.0 mo) and intracranial PFS without increased toxicity, findings that were also supported by Bashir et al.[38,39]

Some studies have highlighted differential response patterns. Shepard et al reported higher complete response rates with concurrent ICI (50% vs 15.6%) without a survival benefit,[40] while Singh et al demonstrated greater tumor shrinkage in larger lesions (>500 mm^3), suggesting size-dependent synergy.[41] Concurrent therapy has also been associated with improved distant intracranial control, particularly with shorter treatment intervals (≤7 d).[42,43] More recent studies by Dohm et al, Frehner et al, and Lu et al further support improved intracranial response with upfront or concurrent SRS, although overall survival benefits remain inconsistent, suggesting a potential role for selective or deferred radiation in asymptomatic patients.[44-46] Key retrospective studies are summarized in **Table 2**.

Importantly, RN and adverse radiation effects remain low (3%-10%) and are not consistently increased with ICI. Established dosimetric factors, particularly V12 Gy, appear to remain the primary drivers of radionecrosis (RN) risk in patients receiving ICIs.[47]

Evidence in RCC

RCC represents a distinct clinical scenario compared with melanoma and NSCLC. Although ICI have improved outcomes in metastatic RCC, intracranial activity remains modest, and local therapy continues to play a central role.[48,49] In the NIVOREN study, nivolumab monotherapy demonstrated limited intracranial efficacy, with an intracranial response rate of 12% and median intracranial progression-free survival of 2.7 months.[48] In contrast, CheckMate 920 reported improved outcomes with nivolumab plus ipilimumab, achieving an objective response rate of 32% and median progression-free survival of 9.0 months in patients with asymptomatic brain metastases.[49] Consequently, SRS remains a cornerstone of management for RCC brain metastases.[50,51] Emerging retrospective data suggest that concurrent SRS and ICI may improve intracranial control and survival without substantially increasing RN risk.[9,13,52] Concurrent ICI has not been associated with increased symptomatic RN, and dosimetric factors such as V12 Gy appear to remain the primary determinants of toxicity.[9,53] However, prospective data defining the optimal integration of SRS and immunotherapy in RCC remain limited.

Evidence From Pooled and Meta-Analyses

Pooled and meta-analytic evidence supports combining SRS with ICI, with stronger and more consistent benefit in melanoma than NSCLC. In melanoma, systematic reviews highlight a shift toward multimodal, patient-specific strategies integrating SRS, immunotherapy, and systemic

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Table 1. Key Retrospective Studies of Stereotactic Radiosurgery Combined With Immune Checkpoint Inhibitors in Melanoma Brain Metastases

STUDY	SAMPLE SIZE	ICI REGIMEN	TREATMENT ARMS	TIMING DEFINITION	RN DEFINITION	RN RISK	KEY EFFICACY + SURVIVAL OUTCOME	KEY TAKEAWAY
Kotecha et al[19]	150 pts / 1003 lesions	PD-1 dominant	SRS + ICI (timing cohorts)	Immediate vs concurrent vs delayed	Radiographic RN; symptomatic cases reported separately	3.2%-3.5%; 7 symptomatic cases	CR ↑ (50% vs 32%); durable response ↑ (94% vs 71%); OS ~30 mo	Timing > toxicity; immediate/ concurrent optimal; steroids detrimental
Minniti et al[28]	80 pts / 326 lesions	PD-1 vs CTLA-4	SRS + nivolumab; SRS + ipilimumab	Concurrent (~1 wk)	MRI/F-DOPA PET-defined RN; Grade 3 RN separately reported	20% (Nivo) vs 29% (Ipi); Grade 3 RN: 9% vs 11%	PFS/LC/OS favor PD-1; OS 22 vs 14.7 mo	PD-1-based SRS associated with better outcomes; higher RN with CTLA-4
Carron et al[27]	50 pts / 188 lesions	PD-1 only	SRS + anti-PD-1	Concurrent ≤3 mo	MRI defined ARE; symptomatic subset reported	4.4% of lesions (8/181); 14.6% of patients (7/48); 6 symptomatic cases (12.5%)	PFS ~13 mo; OS ~16.6 mo (1-yr ~60%)	Favorable survival with low RN; safe PD-1 + SRS
Tang et al[29]	49 pts / 158 lesions	Dual ICI	Nivo + Ipi ± SRS	Concurrent (median 8 d; within 6 wk)	Symptomatic RN only; pathologic confirmation or multidisciplinary review;	6.0% (5/84 lesions)	LC ↑ (92% vs 64%); OS similar (~72% vs 71% at 1 yr)	SRS improves LC without added toxicity; no OS benefit
Fu et al[30]	98 pts	ICI	Concurrent vs non-concurrent SRS + ICI	≤4 wk	CTCAE CNS necrosis/ARE; symptomatic status not specified	2% (concurrent) vs 3% (non-concurrent)	OS ↑ (37 vs 11 mo); PFS ↔	Concurrent ICI improves OS without ↑ RN; edema slightly ↑
Vaios et al[11]	288 pts / 1704 lesions	Dual vs single/no ICI	SRS + dual vs single vs none	Concurrent ≤4 wk	CTCAE grade ≥2 symptomatic RN only; pathologic or clinical-radiographic diagnosis	21.8% (dual ICI) vs 13.5% (single ICI); no ICI 13.7%	RN associated with worse OS	Dual ICI significantly increases RN risk
Mandalà et al[32]	453 pts	Dual ICI (Nivo + Ipi)	Dual ICI ± SRT	Concomitant ≤2 wk	MRI defined RN with clinical follow-up; symptomatic status not specified	10.3% (10.9% sequential vs 9.3% concomitant)	OS ↑ with SRT (27.3/22.2 vs 9.4 mo); no difference between concomitant vs sequential SRT	SRT improves OS regardless of timing
Messing et al[31]	68 pts / 413 lesions	Dual ICI (Nivo + Ipi)	SRS + concurrent dual ICI	≤8 wk	MRI perfusion/ permeability sequences, MR spectroscopy, symptomatic RN only	7% (5 patients)	OS 24 mo; 12-mo 64%, 24-mo 50%; LC ~ 89%	Durable control; prior ICI/targeted therapy predicts worse outcomes

Data extracted and synthesized from cited studies; table created by the authors.

ARE, adverse radiation effects; conc, concurren; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; LC, local control; Nivo, nivolumab; OS, overall survival; PD-1, programmed cell death-1; PFS, progression-free survival; pts, patients; RN, radionecrosis; seq., sequential; SRS, stereotactic radiosurgery; SRT, stereotactic radiation therapy.

Table 2. Key Retrospective Studies of Stereotactic Radiosurgery Combined With Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer Brain Metastases

STUDY	SAMPLE SIZE	ICI REGIMEN	TREATMENT ARMS	TIMING DEFINITION	RN DEFINITION	RN RISK	KEY EFFICACY + SURVIVAL OUTCOME	KEY TAKEAWAY
Yomo et al[38]	585 pts	Mixed ICIs	SRS + ICI vs SRS	Concurrent ≤3 mo	CTCAE v4.0 toxicity grading used	One grade 4 RN, 5 grade 3 RN	mOS 16.9 vs 12.0 mo; HR 0.62; IC-PFS ↑ (35% vs 26%)	Concurrent SRS-ICI associated with improved OS and IC-PFS without ↑ toxicity
Shepard et al[40]	51 pts	PD-1/PD-L1	SRS + ICI vs SRS	ICI within 3 mo	Radiographic RN; included symptomatic RN	Symptomatic RN 2.9% (1/34); no increased RN or intratumoral hemorrhage risk with concurrent ICI	No OS/PFS benefit; CR ↑ (50% vs 15.6%); faster regression	Improved radiographic response without survival benefit
Singh et al[41]	85 pts	Anti–PD-1	SRS + ICI vs SRS + chemo	Variable (subset ≤4 wk)	RN confirmed by histopathology or imaging changes	RN: 10.2% (4/39) vs 10.9% (5/46) (P = 0.7)	No OS benefit (10 vs 11.6 mo); large lesions (>500 mm^3) response ↑ (90% vs 47.8%)	Benefit limited to larger lesions; no overall survival advantage
Singh et al[42]	99 pts	PD-1/PD-L1	SRS + ICI vs SRS + chemo vs SRS + TKI	Concurrent ≤30 d	RN defined by pathology or multidisciplinary MRI review	RN in 34/136 SRS sessions (25%); no increased RN risk with ICI.	1-yr DI-PFS ↑ (67% vs 37% vs 39%); PD-L1 ≥50%: 80%	Concurrent ICI improves intracranial control, especially PD-L1-high
Frehner et al[45]	128 pts	ICI ± chemo	ICI ± chemo + upfront SRT vs ICI ± chemo	Upfront SRT vs none	CTCAE v5.0 CNS adverse events recorded; included symptomatic RN	Symptomatic RN 3.4% (2/58); no fatal CNS adverse events.	iPFS ↑ (12.6 vs 8.2 mo; HR 0.62); no OS benefit (22.8 vs 21.7 mo)	Upfront SRT improves intracranial control; deferral feasible without OS compromise
Chung et al[47]	82 pts	ICI/TKI	Reduced-dose vs standard-dose SRS	Concurrent ≤30 d	Radiographic AREs (radiation necrosis + edema) assessed	AREs: 10.8% vs 23.7% (P = 0.020)	LC similar (94.6% vs 90.3%)	Dose reduction maintains control with lower toxicity

Data extracted and synthesized from the cited studies; table created by the authors.

ARE, adverse radiation effect; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DI-PFS, distant intracranial progression-free survival; ICI, immune checkpoint inhibitor; IC-PFS, intracranial progression-free survival; iPFS, intracranial progression-free survival; LC, local control; OS, overall survival; PFS, progression-free survival; pts, patients; RN, radionecrosis; RN, radionecrosis; SRS, stereotactic radiosurgery; SRT, stereotactic radiation therapy; TKI, tyrosine kinase inhibitor; TKI, tyrosine kinase inhibitor.

therapy.[54] In melanoma, meta-analyses demonstrate significant survival benefit with SRS-ICI, particularly with anti-PD-1 regimens,[55] while Bayesian network analyses rank SRS + ICI as the most effective strategy for overall survival and intracranial control, albeit with increased RN risk.[56] Timing analyses further suggest that concurrent SRS-ICI (within 4 wk) improves survival and intracranial outcomes compared with nonconcurrent approaches.[12,57]

Contemporary pooled data report high local control (80%-85%) and favorable 1-year survival (65%-70%), with RN

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rates of approximately 10% to 12% in the modern immunotherapy era.[58] Importantly, large multicenter analyses indicate that RN risk is primarily driven by dosimetric factors, particularly V12 Gy, rather than treatment timing, supporting the safety of concurrent approaches when appropriate constraints are applied.[9]

In NSCLC, pooled data suggest a more nuanced interaction. Chu et al found no survival advantage with the addition of cranial radiation therapy to ICI, although concurrent treatment reduced distant brain failure.[59] In contrast, Yang et al demonstrated improved overall survival with combined radiation therapy and ICI compared with radiation therapy alone, with concurrent treatment emerging as the optimal strategy without increased toxicity.[60] Collectively in NSCLC, these findings suggest that immunotherapy is the primary driver of survival, whereas SRS primarily enhances intracranial disease control. Major pooled analyses are summarized in **Table 3**.

Comparative Considerations: Melanoma vs NSCLC

Important distinctions exist between melanoma and NSCLC in the context of SRS-ICI integration. In melanoma, evidence consistently supports a synergistic benefit, particularly with concurrent treatment.[12,55,56] In NSCLC, outcomes are more heterogeneous, with immunotherapy driving survival and radiation therapy contributing primarily to intracranial control in a context-dependent manner.[59,60] Molecular subgroups further influence treatment decisions; tumors with actionable driver mutations (e.g., EGFR, ALK) often respond well to CNS-penetrant targeted therapies,[61] and these mutations are less responsive to ICI,[62] limiting the role in SRS-ICI integration in this entity. In these cases, SRS is typically reserved for oligoprogressive or symptomatic disease.

Role of Dosimetry and Treatment Factors

RN following SRS is multifactorial and cannot be attributed to treatment timing alone. While much of the literature focuses on the temporal relationship between SRS and ICI, radiation dose-volume parameters appear to remain the primary determinants of toxicity, particularly with combined-modality therapy.

Among dosimetric parameters, the volume of normal brain receiving 12 Gy (V12 Gy) is the most robust and consistently validated predictor of RN. In a large multicenter analysis by Lehrer et al including 657 patients and over 4000 brain metastases, V12 Gy was independently associated with RN risk, not the timing of ICI administration.[9] Increasing V12 Gy correlates with stepwise toxicity, with low-risk (<12 cm^3), intermediate-risk (12-20 cm^3), and high-risk (>20 cm^3) groups demonstrating progressively higher rates.[9] These findings underscore that dosimetric optimization remains the primary determinant of RN risk, even in the era of immunotherapy.

Additional dosimetric and treatment-related factors contribute to the risk of RN. Treatment of larger lesions (typically >2 cm) requires higher integral dose and results in greater exposure of surrounding normal brain tissue.[47,63,64] In patients with multiple brain metastases, cumulative treated volume increases overall brain dose and expands the low-dose radiation bath.[65] Prior cranial irradiation, including previous SRS or WBRT, further reduces normal tissue tolerance and may further increase the risk of RN.[66]

Clinical factors, including baseline edema, corticosteroid use, and lesion location, particularly in eloquent or deep brain regions, may influence both the risk and clinical impact of RN.[67,68] These factors may interact with immunotherapy, as immune activation can amplify inflammatory responses.

Overall, these findings support a shift in clinical thinking. RN risk should not be viewed solely through treatment timing, but rather through an integrated framework incorporating dosimetry, lesion characteristics, prior treatment, and immunotherapy regimen. In particular, patients with high-risk dosimetric features (e.g., elevated V12 Gy or large target volume) combined with clinical modifiers such as dual checkpoint blockade or significant perilesional edema may warrant treatment modification strategies, including dose optimization and hypofractionation.

Fractionation and Risk Mitigation Strategies

Hypofractionated stereotactic radiation therapy is commonly employed to mitigate the risk of RN, particularly for lesions >2 cm or when V12 Gy exceeds approximately 10 cm^3,[64] or those receiving dual immune checkpoint inhibition.[9] Although prospective data remain limited, this approach is widely adopted in clinical practice. By reducing peak dose to normal brain tissue, fractionation may help offset the increased inflammatory effects associated with concurrent immunotherapy.

Radiographic Assessment and Diagnostic Challenges

Distinguishing pseudoprogression, RN, and true tumor progression after SRS in patients receiving ICIs remains a major diagnostic challenge, as all may present with enlarging contrast-enhancing lesions on MRI.[69,70] Pseudoprogression typically occurs early in the first few months (approximately 6 months), whereas RN is a delayed effect, often developing 6 to 12 months post SRS.[71-73] The combined inflammatory effects of SRS and immunotherapy further complicate interpretation. The iRANO criteria recommend confirmatory imaging within 6 months of ICI initiation.[74] Advanced imaging modalities, including perfusion MRI and amino acid PET, improve diagnostic accuracy,

Table 3. Systematic Review and Meta-Analytic Evidence on Stereotactic Radiosurgery and Immunotherapy in Melanoma and Non-Small Cell Lung Cancer Brain Metastases

STUDY	PREDOMINANT HISTOLOGY	SAMPLE SIZE	ICI REGIMEN	TREATMENT ARMS	RISK OF RADIONECROSIS	EFFICACY AND SURVIVAL OUTCOME	KEY TAKEAWAYS
Lehrer et al[12]	Mixed (melanoma dominant)	17 studies; 534 pts	CTLA-4, PD-1	Concurrent vs non-concurrent SRS + ICI	RN ~5.3%	1-yr OS: 64.6% vs 51.6%; improved LC	Early evidence supporting concurrent SRS + ICI
Badrigilan et al[57]	Predominantly melanoma	16 studies; 1356 pts	Mostly CTLA-4, some PD-1	SRS + ICI vs SRS; timing comparisons	No significant increase	Improved OS and local control	Supports concurrent strategy without clear toxicity increase
Chu et al[59]	NSCLC	46 trials; 3160 pts	PD-1, PD-L1, CTLA-4	ICI vs ICI + RT; SRS vs WBRT	Not primary endpoint	PFS HR ~0.48; OS HR ~0.64; ↓ DBF (OR 0.15)	ICI drives survival; RT improves intracranial control
Yang et al[60]	NSCLC	19 studies	PD-1/PD-L1/ CTLA-4	RT + ICI vs RT alone	No ↑ grade 3-4 toxicity	OS improved (HR ~0.77 vs RT alone)	Adding ICI to RT improves survival
Lehrer et al[12]	Mixed (melanoma, NSCLC, RCC)	657 pts; 4182 mets	PD-1, PD-L1, CTLA-4	Concurrent vs non-concurrent SRS + ICI	RN ~ 10 %; symptomatic ~6%-7%	No major OS difference by timing	RN driven by dosimetry (V12 Gy)
Williams et al[55]	Melanoma	126 studies; ~6500 pts	Anti–PD-1, CTLA-4, mixed	SRS + ICI vs SRS or ICI alone	Not consistently reported	~30%-65% reduction in mortality risk	Strong survival benefit with SRS + ICI
Li et al[56]	Melanoma	10 studies; 836 pts	ICI ± targeted therapy	SRS + ICI vs SRS alone or ICI alone	Higher RN risk with SRS + ICI vs SRS alone	OS improved vs SRS alone (HR ~0.64); intracranial PFS improved vs ICI alone (HR ~0.66)	SRS + ICI ranked best for OS and intracranial control
Grant et al[54]	Melanoma	70 studies	ICI, targeted therapy	Multimodal approaches	Low neurotoxicity	mOS ~5-16 months	Supports multimodal integration
Ahmadvand et al[58]	Mixed	16 studies; 1529 pts	PD-1/PD-L1 inhibitors	SRS + ICI	RN ~12 %; ARE ~31%	LC ~84% (12 mo); 1-yr OS ~67%	High control with measurable RN risk

Data extracted and synthesized from pooled and meta-analytic studies; table created by the authors.

ARE, adverse radiation effects; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DBF, distant brain failure; HR, hazard ratio; ICI, immune checkpoint inhibitor; LC, local control; mOS, median overall survival; NSCLC, non-small cell lung cancer.; OR, odds ratio; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; RCC, renal cell carcinoma; RN, radionecrosis; SRS, stereotactic radiosurgery.

though uncertainty often necessitates multidisciplinary evaluation and serial imaging.[69] Amino acid PET tracers, particularly fluoroethyltyrosine PET and methionine PET, provide greater specificity than conventional MRI for distinguishing RN from tumor progression and are increasingly used in contemporary diagnostic algorithms.[69,75,76]

Comparison of reported RN rates across studies is limited by heterogeneity in diagnostic criteria and outcome definitions. Some studies report only symptomatic RN, whereas others include

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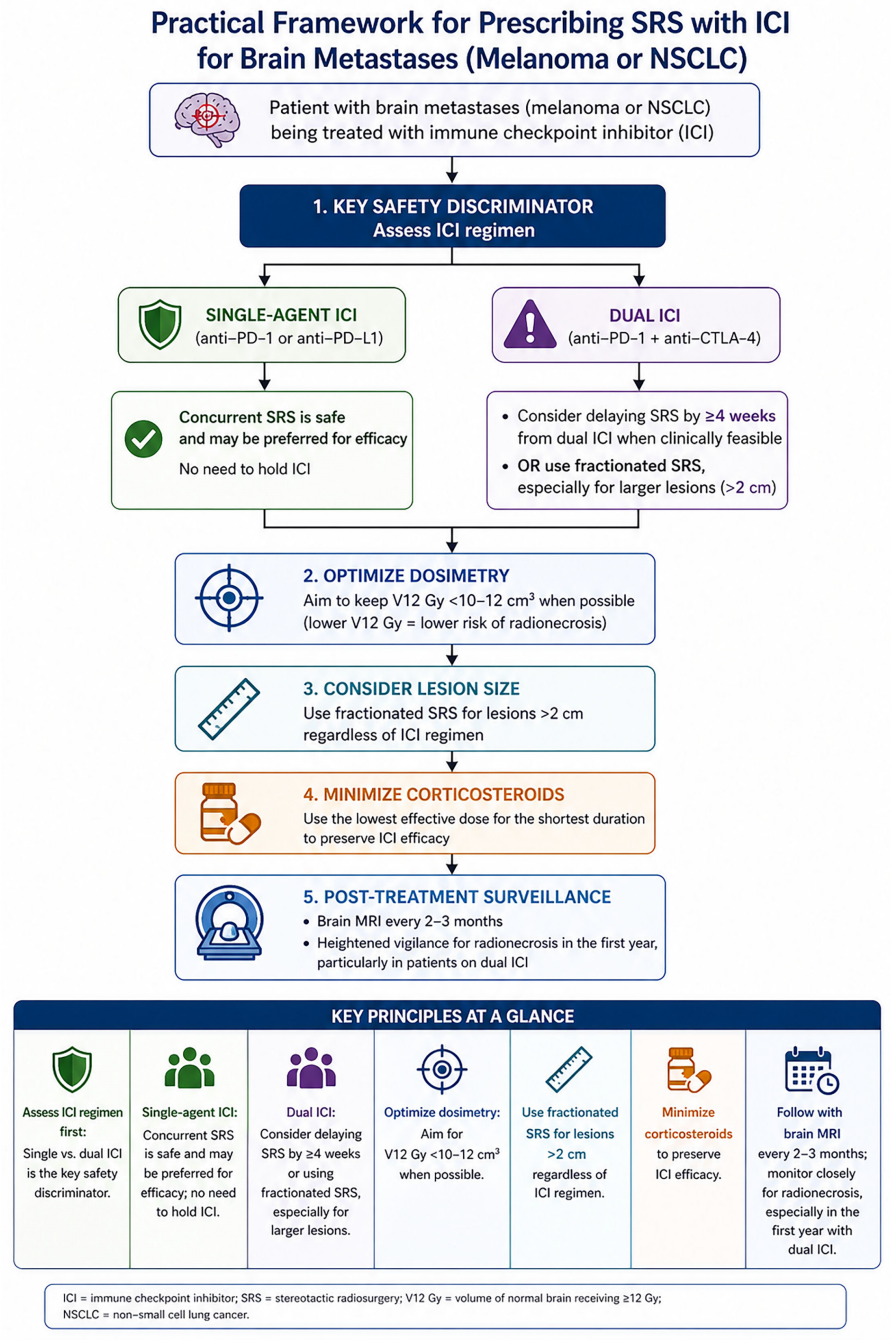
Figure 1. Practical framework for prescribing stereotactic radiosurgery (SRS) with immune checkpoint inhibitors (ICIs) for brain metastases from melanoma or non–small cell lung cancer (NSCLC). The algorithm highlights ICI regimen as the primary safety discriminator, favoring concurrent SRS with single-agent anti–PD-1/PD-L1 therapy and consideration of delayed or fractionated SRS with dual ICI therapy (anti–PD-1 plus anti–CTLA-4).



asymptomatic radiographic changes or broader adverse radiation effects, likely contributing to variability in reported RN incidence. Studies reporting only symptomatic RN generally demonstrate lower rates than those incorporating radiographic or asymptomatic RN. Therefore, RN rates should be interpreted with caution when comparing outcomes across studies.

Management of RN

Management of RN after SRS follows a stepwise, symptom-guided approach. Asymptomatic cases may be observed with serial imaging, while symptomatic patients are treated with corticosteroids using the lowest effective dose and gradual taper. Bevacizumab is effective in steroid-refractory cases, with response rates exceeding 80% and significant radiographic improvement.[77-79] Emerging evidence suggests that Boswellia serrata reduces RN-associated edema, with a retrospective series reporting radiographic improvement in approximately 60% of patients and a favorable safety profile, although prospective validation is needed.[80] Surgical resection or laser interstitial thermal therapy (LITT) is reserved for refractory or diagnostically uncertain cases, providing tissue confirmation and durable control.[81] Emerging data suggest comparable efficacy between bevacizumab and LITT.[82] Management should be individualized based on symptoms, lesion characteristics, and diagnostic certainty.

Limitations of Current Evidence

The current literature is limited by its predominantly retrospective nature, heterogeneity in study design, and variability in definitions of concurrent treatment. Confounding by indication and challenges in distinguishing RN from tumor progression further complicate interpretation.

Practical Clinical Implications

The integration of SRS with ICI in clinical practice requires a structured, risk-adapted approach that incorporates

immunotherapy regimen, dosimetric parameters, lesion characteristics, and patient-specific factors.

Concurrent SRS with single-agent ICI is generally well tolerated and may enhance local control without a substantial increase in RN risk.[19] In this context, concurrent or near concurrent SRS, typically within 2 to 4 weeks, is a reasonable and commonly adopted approach. In contrast, dual checkpoint blockade may be associated with an increased risk of symptomatic RN in some studies, although the evidence remains heterogeneous and warrants a more cautious integration strategy.[11] For these patients, delayed SRS by ≥4 weeks or the use of hypofractionated regimens should be considered, particularly for larger lesions or those with high-risk features.[11]

The volume of normal brain receiving 12 Gy (V12 Gy) has been one of the most consistently validated predictors of RN in SRS literature and remains highly relevant in patients receiving concurrent immunotherapy.[9] Efforts to minimize normal brain dose are essential, with V12 Gy thresholds serving as a practical guide for risk stratification. Hypofractionated SRS should be considered for lesions greater than 2 cm[83] or when V12 Gy constraints cannot be met, particularly in patients receiving dual ICI.

Additional factors, including baseline edema, corticosteroid use, prior cranial irradiation, and intracranial disease burden, may influence efficacy and toxicity and should inform individualized treatment planning. Minimizing corticosteroid exposure is particularly important given its potential impact on immunotherapy efficacy.[84]

Overall, optimal integration of SRS and ICI requires a composite clinical framework that prioritizes immunotherapy regimen, dosimetric risk, and lesion characteristics rather than relying on treatment timing alone. A practical decision-making framework is summarized in (**Figure 1**).

Future Directions

Future research efforts should focus on prospective trials to define optimal timing and sequencing, alongside strategies such as dose de-escalation and fractionation to reduce toxicity.[25,47] Emerging biomarkers, including neutrophil-to-lymphocyte ratio, early $CD8^+$ T-cell activation, tumor aneuploidy, and immune-inflammatory signatures, may help identify patients most likely to benefit from combined therapy and guide immunotherapy selection.[16,85] Additional areas include exploiting the abscopal effect,[86] novel immune targets, advanced imaging, and multimodality approaches.[87-89]

Conclusion

The integration of SRS and ICIs represents a major advance in the management of brain metastases. Concurrent SRS with single-agent ICI appears feasible and may enhance intracranial control without significantly increasing toxicity. In contrast, dual checkpoint blockade and higher dose volume exposure (particularly V12 Gy) define a higher-risk population for RN, necessitating more cautious, individualized strategies. Optimal integration requires consideration of not only timing, but also immunotherapy regimen, lesion characteristics, fractionation, and dosimetric parameters. Prospective studies are needed to define these relationships and guide evidence-based clinical decision-making.

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