Review

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Stereotactic Radiosurgery and Immunotherapy for 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 radiotherapy. Immune checkpoint inhibitors (ICIs) have also transformed systemic therapy for tumors with central nervous system involvement, creating 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 (RN) with concurrent single-agent ICI; however, emerging data suggest that dual checkpoint blockade may increase the risk of symptomatic RN.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 RN 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: brain metastases; stereotactic radiosurgery; immune checkpoint inhibitors; melanoma; non-small cell lung cancer; radionecrosis; treatment timing

1. 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, 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 whole-brain radiotherapy (WBRT) in appropriately selected patients [5].

SRS is now a standard treatment for limited brain metastases, delivering highly conformal, ablative doses with high local control while preserving neurocognitive function compared with WBRT [6]. Concurrently, ICIs have transformed systemic therapy for melanoma, NSCLC, and other

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malignancies with central nervous system involvement [7]. As a result, patients increasingly receive both SRS and ICIs during their treatment course [8].

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 [9]. However, this immune activation may also increase inflammatory toxicity, including RN and edema [10].

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 [11,12].

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.

2. 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 radiotherapy," "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.

3. Biological Rationale for Combining SRS and Immunotherapy

The rationale for combining SRS with immune checkpoint inhibitors (ICIs) is based on radiation induced immune modulation [9]. High-dose focal radiation can induce immunogenic cell death, promoting antigen release, enhanced antigen presentation, and subsequent dendritic cell activation and T-cell priming, effectively transforming the irradiated lesion into an in situ vaccine–like stimulus [13,14].

Radiation also modulates the tumor microenvironment by increasing major histocompatibility complex (MHC) expression, enhancing T-cell infiltration, and altering cytokine signaling [15]. These effects may augment ICI efficacy, which functions by relieving inhibitory signals on T cells and sustaining antitumor immune responses [16]. This biologic synergy supports combining SRS and ICIs, particularly when delivered in close temporal proximity [17–19] .

However, these same mechanisms may also increase toxicity. Radionecrosis (RN) is a multifactorial process involving vascular injury, hypoxia, and immune-mediated inflammation [20]. ICIs may amplify these pathways, particularly with dual checkpoint blockade, potentially increasing the risk of treatment-related toxicity [10].

4. Clinical Evidence on Treatment Timing

4.1. 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 [18].

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Despite this variability, most studies adopt a practical definition of concurrent therapy as SRS delivered within approximately 2–4 weeks of ICI administration [8,12]. 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 [18].

4.2. Evidence in Melanoma

Radiation may potentiate ICI through enhanced antigen presentation and T-cell activation, providing a biological rationale for combining SRS with ICI [21]. Dual ICI remains the systemic backbone in melanoma, with Tawbi et al. demonstrating intracranial response rates of 55–57% and durable control [22]. Subsequent SRS-ICI studies consistently show improved intracranial control. Kotecha et al. reported that timing influences efficacy more than toxicity, with concurrent ICI improving response and low RN(3–5%) [18], while Carron et al. confirmed low toxicity with anti–PD-1 therapy (adverse radiation effect 4–5%, symptomatic <3%) [23].

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 (15–25%) [24]. In contrast, Tang et al. demonstrated significantly improved local control (92% vs 64%) without excess toxicity or increased RN [25]. Fu et al. similarly observed improved survival with concurrent SRS–ICI (37.1 vs 11.4 months) without increased radiation toxicity (2–3%) [26]. 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 [27]. Conversely, Vaios et al. reported higher RN rates with dual ICI (20–25%) [10], whereas Mandalà et al. demonstrated survival benefit with moderate RN (10%) [28]. Key retrospective studies are summarized in Table 1.

Table 1. Key retrospective studies of SRS combined with immune checkpoint inhibitors in melanoma brain metastases.

Table 1. Retrospective Studies on SRS and Systemic Therapy (Melanoma Focus)

Study (Year)	Sample Size	ICI Regimen	Treatment Arms	Timing Definition	RN Risk	Key Efficacy + Survival Outcome	Key Takeaway
Kotecha et al. (2019) [18]	150 pts / 1003 lesions	PD-1 dominant	SRS + ICI (timing cohorts)	Immediate vs concurrent vs delayed	~3–5%	CR ↑ (50% vs 32%); durable response ↑ (~94% vs 71%); OS ~30 mo	Timing > toxicity; immediate/concurrent optimal; steroids detrimental
Minniti et al. (2019) [24]	80 pts / 326 lesions	PD-1 vs CTLA-4	SRS + nivolumab; SRS + ipilimumab	Concurrent (~1 week)	~15–25% (higher with CTLA-4)	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. (2020) [23]	50 pts / 188 lesions	PD-1 only	SRS + anti–PD-1	Concurrent ≤3 mo	~4–6% ARE	PFS ~13 mo; OS ~16.6 mo (1-yr ~60%)	Favorable survival with low RN; safe PD-1 + SRS
Tang et al. (2024) [25]	49 pts / 158 lesions	Dual ICI (Nivo + Ipi)	Nivo + Ipi ± SRS	Concurrent	No ↑ toxicity	LC ↑ (92% vs 64%); OS similar (~72% vs 71% at 1 yr)	SRS improves LC without added toxicity; no OS benefit
Fu et al. (2025) [26]	98 pts	ICI	Concurrent vs non-concurrent SRS + ICI	≤4 weeks	RN 2% vs 3%	OS ↑ (37 vs 11 mo); PFS ↔	Concurrent ICI improves OS without ↑ RN; edema slightly ↑
Vaios et al. (2025) [10]	288 pts / 1704 lesions	Dual vs single/no ICI	SRS + dual vs single vs none	Concurrent ≤4 weeks	RN: 21.8% (dual) vs 13.5% (single) vs 13.7% (none)	RN associated with worse OS	Dual ICI significantly increases RN risk
Mandalà et al. (2025) [28]	453 pts	Dual ICI (Nivo + Ipi)	Dual ICI ± SRT (concomitant vs sequential)	Concomitant ≤2 weeks	~10% (no timing difference)	OS ↑ with SRT (27.3/22.2 vs 9.4 mo); no diff conc vs seq	SRT improves OS regardless of timing
Messing et al. (2026) [27]	68 pts / 413 lesions	Dual ICI (Nivo + Ipi)	SRS + concurrent dual ICI	≤8 weeks	~7%	OS 24 mo; 12-mo 64%, 24-mo 50%; LC excellent (~89%)	Durable control; prior ICI/targeted therapy predicts worse outcomes

Abbreviations: SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; ICI, immune checkpoint inhibitor; PD-1, programmed cell death-1; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; Nivo, nivolumab; Ipi, ipilimumab; CR, complete response; LC, local control; PFS, progression-free survival; OS, overall survival; RN, radionecrosis; ARE, adverse radiation effects; mo, months; conc, concurrent; seq, sequential.

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

Overall, the evidence is heterogeneous and predominantly retrospective but supports close temporal integration of SRS with ICI to optimize intracranial control. ICI regimen and prior therapy exposure appear to be key determinants of toxicity and outcomes, underscoring the need for prospective validation.

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4.3. Evidence in Non-Small Cell Lung Cancer (NSCLC)

Non–small cell lung cancer (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, although they were not designed to define optimal sequencing [29–32].

Across retrospective cohorts, SRS combined with ICI consistently improves intracranial control and, in selected studies, overall survival, with outcomes influenced by timing and patient selection. Foundational studies by Chen et al. and Schapira et al. showed that concurrent SRS–ICI (within 2–4 weeks) is associated with improved survival and intracranial control compared with nonconcurrent approaches [12,33]. Larger analyses, including Yomo et al., confirmed a survival advantage (mOS ~16.9 vs. 12.0 months) and improved intracranial PFS without increased toxicity [34], consistent with findings from Bashir et al. [35].

Some studies highlight differential response patterns. Shepard et al. found no survival benefit but significantly higher complete response rates (50% vs. 15.6%) with concurrent ICI [36], while Singh et al. demonstrated greater tumor shrinkage in larger lesions (>500 mm^3), suggesting size-dependent synergy [37]. Additional data show improved distant intracranial control with concurrent therapy, with shorter treatment intervals (≤7 days) associated with superior outcomes [38,39]. More recent studies (Dohm et al., Frehner et al., Lu et al.) support improved intracranial response with upfront or concurrent SRS, although overall survival differences remain inconsistent, indicating a potential role for selective or deferred radiation in asymptomatic patients [40–42]. Key retrospective studies are summarized in Table 2.

Table 2. Key retrospective studies of SRS combined with immune checkpoint inhibitors in NSCLC brain metastases.

Table 2. Retrospective Studies on SRS and Immunotherapy (NSCLC Focused)

Study (Year)	Sample Size	ICI Regimen	Treatment Arms	Timing Definition	RN Risk	Key Efficacy + Survival Outcome	Key Takeaway
Yomo et al. (2023) [34]	585 pts	Mixed ICIs	SRS + ICI vs SRS	Concurrent ≤3 mo	No ↑ G3–4 toxicity	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. (2020) [36]	51 pts	PD-1/PD-L1	SRS + ICI vs SRS	ICI within 3 mo	RN 5.9% vs 2.9%; no ↑	No OS/PFS benefit; CR ↑ (50% vs 15.6%); faster regression	Improved radiographic response without survival benefit
Singh et al. (2020) [37]	85 pts	Anti–PD-1	SRS + ICI vs SRS + chemo	Variable (subset ≤4 wk)	RN ~10% both arms	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 SA et al. (2020) [38]	99 pts	PD-1/PD-L1	SRS + ICI vs SRS + chemo vs SRS + TKI	Concurrent ≤30 d	No ↑ RN	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. (2025) [41]	128 pts	ICI ± chemo	ICI ± chemo + upfront SRT vs ICI ± chemo	Upfront SRT vs none	Very low; 2 CNS AEs	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. (2026) [43]	82 pts	ICI/TKI	Reduced-dose vs standard-dose SRS	Concurrent ≤30 d	ARE ↓ (10.8% vs 23.7%)	LC similar (94.6% vs 90.3%)	Dose reduction maintains control with lower toxicity

Abbreviations: SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; RN, radionecrosis; ARE, adverse radiation effect; OS, overall survival; PFS, progression-free survival; IC-PFS, intracranial progression-free survival; DI-PFS, distant intracranial progression-free survival; iPFS, intracranial progression-free survival; CR, complete response; LC, local control; mo, months.

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

Importantly, radionecrosis and adverse radiation effects remain low (~3–10%) and are not consistently increased with ICI. Emerging evidence suggests that dosimetric factors, rather than ICI itself, are the primary determinants of toxicity [43].

4.4. Evidence from Pooled and Meta-Analyses

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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 therapy [44]. In melanoma, meta-analyses demonstrate significant survival benefit with SRS–ICI, particularly with anti–PD-1 regimens [45], while Bayesian network analyses rank SRS + ICI as the most effective strategy for overall survival and intracranial control, albeit with increased radionecrosis (RN) risk [46]. Timing analyses further suggest that concurrent SRS–ICI (within 4 weeks) improves survival and intracranial outcomes compared with nonconcurrent approaches [11,47].

Contemporary pooled data report high local control (80–85%) and favorable 1-year survival (65–70%), with RN rates of approximately 10–12% in the modern immunotherapy era [48]. 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 [8].

In NSCLC, pooled data suggest a more nuanced interaction. Chu et al. found no significant difference in survival between ICI alone and ICI combined with cranial radiotherapy, although concurrent treatment reduced distant brain failure [49]. In contrast, Yang et al. demonstrated improved overall survival with combined radiotherapy and ICI compared with radiotherapy alone, with concurrent treatment emerging as the optimal strategy without increased toxicity [50]. These findings reflect different clinical questions—whether radiotherapy augments ICI or vice versa—and collectively support a model in which immunotherapy drives survival, while SRS improves intracranial disease control.

Overall, SRS–ICI integration provides the greatest benefit in melanoma, particularly with concurrent delivery. In NSCLC, immunotherapy is the primary driver of survival, while SRS optimizes intracranial control. Major pooled analyses are summarized in Table 3.

Table 3. Summary of pooled analyses and meta-analyses evaluating SRS–ICI integration in brain metastases.

Table 3. Pooled and Meta-Analytic Evidence on SRS and Immunotherapy in Melanoma and NSCLC Brain Metastases

Study (year)	Predominant histology	Sample size	ICI regimen	Treatment arms	Risk of radionecrosis	Efficacy and survival outcome	Key takeaways
Lehrer et al. (2019) [11]	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. (2022) [47]	Predominantly melanoma	16 studies; 1,356 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. (2022) [49]	NSCLC	46 trials; 3,160 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. (2022) [50]	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. (2023) [8]	Mixed (melanoma, NSCLC, RCC)	657 pts; 4,182 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. (2024) [45]	Melanoma	126 studies; ~6,500 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. (2024) [46]	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. (2025) [44]	Melanoma	70 studies	ICI, targeted therapy	Multimodal approaches	Low neurotoxicity	mOS ~5–16 months	Supports multimodal integration
Ahmadvand et al. (2025) [48]	Mixed	16 studies; 1,529 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

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

Source: Data summarized from pooled and meta-analytic studies evaluating SRS and immunotherapy in melanoma and NSCLC brain metastases (references 8, 11, 44–50).

4.5. 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 [11,45,46]. In NSCLC, outcomes are more heterogeneous, with immunotherapy driving survival and radiotherapy contributing primarily to intracranial control in a context-

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dependent manner [49,50]. Molecular subgroups further influence treatment decisions; tumors with actionable driver mutations (e.g., EGFR, ALK) often respond well to CNS-penetrant targeted therapies [51] and these mutations are less responsive to ICI [52], limiting the role in SRS–ICI integration in this entity. In these cases, SRS is typically reserved for oligoprogressive or symptomatic disease.

5. Role of Dosimetry and Treatment Factors

Radionecrosis following stereotactic radiosurgery is multifactorial and cannot be explained by treatment timing alone. Although much of the literature focuses on the temporal relationship between SRS and ICI, accumulating evidence suggests that radiation dose volume parameters remain the primary determinants of toxicity, particularly in the setting of 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 radionecrosis. In a large multicenter analysis by Lehrer et al. including 657 patients and over 4,000 brain metastases, V12 Gy was independently associated with radionecrosis risk not the timing of ICI administration (8). 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 [8]. These findings underscore that dosimetric optimization remains the primary determinant of radionecrosis risk, even in the era of immunotherapy.

Additional dosimetric and treatment related factors contribute to the risk of radionecrosis. Treatment of larger lesions (typically >2 cm) requires higher integral dose and results in greater exposure of surrounding normal brain tissue [43,53,54]. In patients with multiple brain metastases, cumulative treated volume increases overall brain dose and expands the low-dose radiation bath [55]. Prior cranial irradiation, including previous SRS or WBRT, further reduces normal tissue tolerance and may further increase the risk of radionecrosis [56].

Clinical factors are equally relevant. Baseline edema, corticosteroid use, and lesion location particularly in eloquent or deep brain regions may influence both the development and clinical impact of radionecrosis [57,58]. These factors may interact with immunotherapy, as immune activation can amplify inflammatory responses.

The addition of ICIs introduces further complexity. While single agent ICIs do not appear to substantially increase radionecrosis risk [23], emerging data suggest that dual checkpoint blockade may enhance inflammatory toxicity, making dosimetric optimization even more critical [10].

Overall, these findings support a shift in clinical thinking. Radionecrosis risk should not be viewed primarily through treatment timing, but rather through an integrated framework of dosimetry, lesion characteristics, prior treatment, and immunotherapy regimen. In particular, the combination of high risk dosimetric features (e.g., elevated V12 Gy or large target volume) with clinical modifiers such as dual checkpoint blockade or significant perilesional edema defines a higher risk population in whom treatment modification strategies, including dose optimization and hypofractionation, should be considered.

6. Fractionation and Risk Mitigation Strategies

Hypofractionated stereotactic radiotherapy is commonly employed to mitigate the risk of radionecrosis, particularly for lesions >2 cm or when V12 Gy exceeds approximately 10 cm^3 [54], or those receiving dual immune checkpoint inhibition [8]. Although prospective data remains 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.

7. Radiographic Assessment and Diagnostic Challenges

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Distinguishing pseudoprogression, radionecrosis, and true tumor progression after SRS in patients receiving immune checkpoint inhibitors remains a major diagnostic challenge, as all may present with enlarging contrast enhancing lesions on MRI [59,60]. Pseudoprogression typically occurs early in first few months (approximately 6 months), whereas radionecrosis is a delayed effect, often developing 6–12 months post SRS [61–63]. The combined inflammatory effects of SRS and immunotherapy further complicate interpretation. The iRANO criteria recommend confirmatory imaging within 6 months of ICI initiation [64]. Advanced imaging modalities, including perfusion MRI and amino acid PET, improve diagnostic accuracy, though uncertainty often necessitates multidisciplinary evaluation and serial imaging [59].

8. Management of Radionecrosis

Management of radionecrosis 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 [65–67]. Surgical resection or laser interstitial thermal therapy (LITT) is reserved for refractory or diagnostically uncertain cases, providing tissue confirmation and durable control [68]. Emerging data suggest comparable efficacy between bevacizumab and LITT [69]. Management should be individualized based on symptoms, lesion characteristics, and diagnostic certainty.

9. 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 radionecrosis from tumor progression further complicate interpretation.

10. Practical Clinical Implications

The integration of SRS and immune checkpoint inhibitors requires a structured, risk-adapted approach incorporating immunotherapy regimen, dosimetry, and clinical factors.

10.1. Immunotherapy Regimen

The distinction between single agent and dual checkpoint inhibition is critical. Concurrent SRS with single agent ICI appears safe and may improve intracranial outcomes without significantly increasing radionecrosis risk. In contrast, dual checkpoint blockade is associated with a higher incidence of symptomatic radionecrosis and should prompt more cautious integration strategies.

10.2. Timing Considerations

For single-agent ICI, concurrent or near-concurrent SRS (within approximately 2–4 weeks) is reasonable and may enhance response and local control. With dual ICI, the risk of radionecrosis is higher and optimal sequencing remains uncertain; when feasible, delaying SRS by ≥4 weeks or using fractionated SRS should be considered, particularly for larger or high-risk lesions.

10.3. Dosimetric Risk

Radiation dose volume parameters, particularly V12 Gy, remain the dominant predictors of radionecrosis. Efforts should be made to minimize normal brain dose, with V12 Gy thresholds serving as a practical guide for risk stratification.

10.4. Fractionation Strategy

Radiation dose–volume parameters, particularly V12 Gy, remain the dominant predictors of radionecrosis and should guide risk stratification and treatment planning.

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10.5. Additional Clinical Modifiers

Corticosteroid use, baseline edema, prior cranial irradiation, and cumulative intracranial disease burden further influence both efficacy and toxicity and should be incorporated into decision-making.

10.6. Integrated Clinical Approach

Treatment decisions should be guided by a composite assessment of ICI regimen, lesion characteristics, and dosimetry, with selective use of fractionation and minimization of corticosteroids. Coordination of systemic and local therapy should prioritize both efficacy and toxicity mitigation rather than timing alone.

A practical decision framework for integrating SRS with single-agent or dual ICI is summarized in Figure 1.

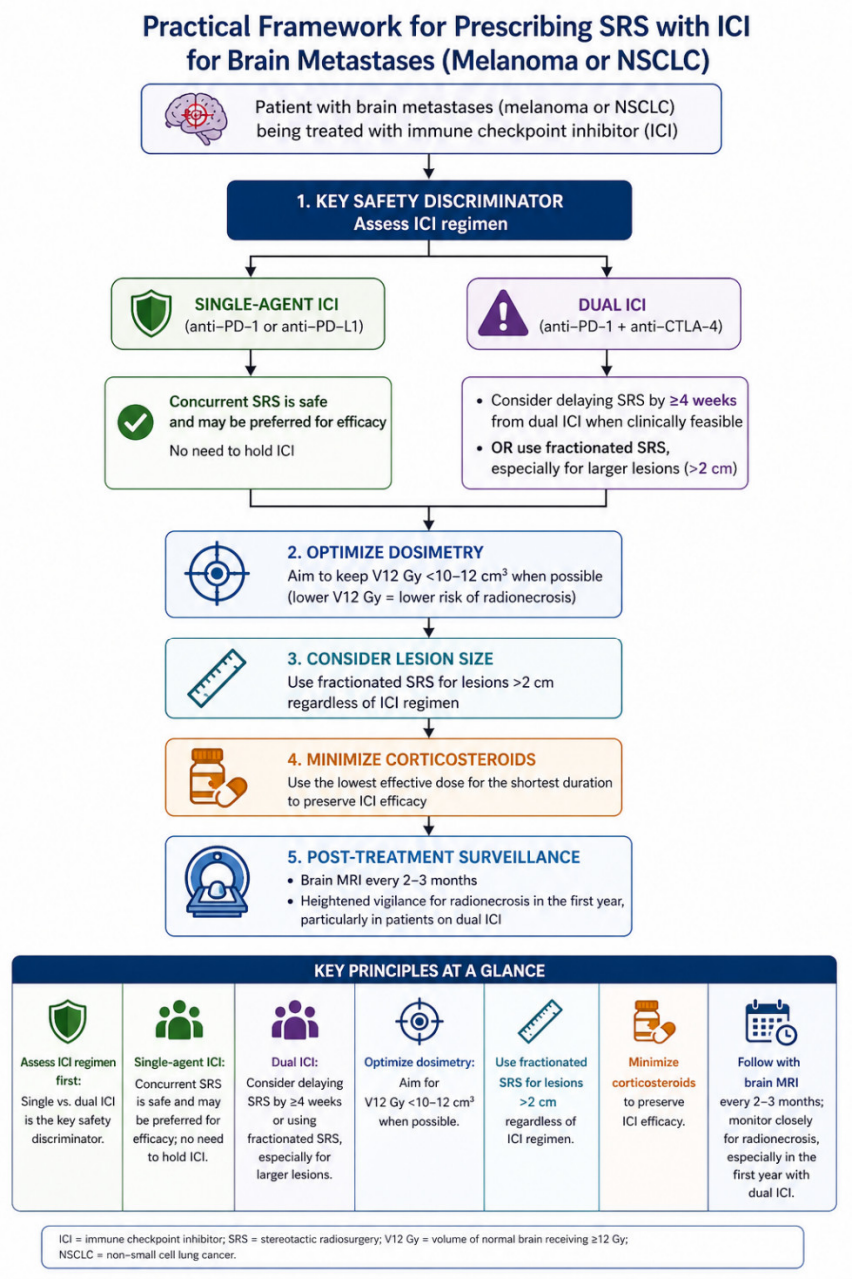

Figure 1. Practical framework for integrating SRS with immune checkpoint inhibitors in brain metastases. This schema.

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11. Future Directions

Future directions include prospective trials to define optimal timing and sequencing, alongside strategies such as dose de-escalation and fractionation to reduce toxicity [43,70]. Emerging biomarkers including neutrophil to lymphocyte ratio, early $CD8^+$ T-cell activation, tumor aneuploidy, and immuno-inflammatory signatures may help identify patients most likely to benefit from combined therapy and guide immunotherapy selection [15,71]. Additional areas include exploiting the abscopal effect [72], novel immune targets, advanced imaging, and multimodality approaches [73–75].

12. Conclusions

The integration of SRS and immune checkpoint inhibitors 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 radionecrosis, 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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