

Stereotactic Radiosurgery Versus Whole-Brain Radiotherapy in Patients with Multiple Brain Metastases: Current Evidence and Future Perspectives

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<https://doi.org/10.5281/zenodo.21448795>

Received: 10 June 2026, Accepted: 25 June 2026, Online First: 20 July 2026

ABSTRACT

Brain metastases are among the most common intracranial tumors in adults and represent a major cause of morbidity and mortality in patients with advanced cancer. Historically, whole-brain radiotherapy (WBRT) has been the standard treatment for patients with multiple brain metastases because of its ability to address both visible and microscopic intracranial disease. However, concerns regarding radiation-induced neurocognitive decline and reduced quality of life have led to increasing interest in stereotactic radiosurgery (SRS), a highly precise radiation technique that delivers ablative doses to metastatic lesions while minimizing exposure to surrounding healthy brain tissue. Recent prospective studies, randomized controlled trials, and meta-analyses have demonstrated that SRS alone provides local tumor control and overall survival outcomes comparable to WBRT in selected patients with multiple brain metastases, while significantly preserving cognitive function and maintaining quality of life. Advances in imaging, treatment planning, and radiation delivery have further expanded the role of SRS beyond patients with a limited number of lesions, challenging the traditional paradigm that favored WBRT for extensive intracranial disease. Additionally, the emergence of hippocampal-avoidance WBRT and neuroprotective agents such as memantine has improved the therapeutic ratio of WBRT, although concerns regarding long-term cognitive toxicity remain. This review summarizes current evidence comparing SRS and WBRT with respect to treatment efficacy, intracranial control, neurocognitive outcomes, toxicity profiles, and patient-reported quality of life. Furthermore, it discusses evolving treatment strategies, integration with systemic therapies, technological innovations, and future research directions aimed at optimizing personalized care for patients with multiple brain metastases.

Keywords: *Brain metastases; Stereotactic radiosurgery; Whole-brain radiotherapy; Neurocognition; Quality of life; Brain tumors; Radiation oncology*

INTRODUCTION

Brain metastases represent the most common intracranial malignancies in adults and are a major cause of cancer-related morbidity and mortality worldwide. Approximately 20–40% of patients with systemic malignancies develop brain metastases during the course of their disease, with lung cancer, breast cancer, melanoma, renal cell carcinoma, and colorectal cancer being the most common primary tumors. Advances in systemic therapies and improved neuroimaging have increased the detection and survival of patients with brain

metastases, thereby making optimal intracranial management increasingly important.

Whole-brain radiotherapy (WBRT) has historically been considered the standard treatment for patients with multiple brain metastases because of its ability to treat both visible lesions and microscopic intracranial disease. However, WBRT is associated with significant neurocognitive impairment, particularly deficits in memory, executive function, and quality of life. These concerns have shifted clinical practice toward stereotactic radiosurgery (SRS), which delivers highly conformal, high-dose radiation to metastatic lesions while

minimizing radiation exposure to surrounding healthy brain tissue.

Recent randomized clinical trials, prospective cohort studies, and international guidelines have expanded the role of SRS beyond patients with only a few brain metastases. Growing evidence suggests that treatment decisions should be based not only on the number of lesions but also on total intracranial tumor volume, patient performance status, extracranial disease control, molecular characteristics, and expected survival.

The purpose of this review is to critically evaluate current evidence comparing stereotactic radiosurgery and whole-brain radiotherapy for patients with multiple brain metastases, with emphasis on treatment efficacy, intracranial control, neurocognitive outcomes, quality of life, toxicity, current international guidelines, and future therapeutic directions.

HIGHLIGHTS

- Stereotactic radiosurgery provides excellent local tumor control while preserving neurocognitive function.
- Whole-brain radiotherapy offers superior intracranial disease control but is associated with greater cognitive toxicity.
- Hippocampal-avoidance WBRT combined with memantine significantly reduces radiation-induced cognitive decline.
- Current international guidelines increasingly support SRS for selected patients with up to 10 brain metastases.
- Future treatment strategies focus on personalized therapy integrating SRS, systemic therapies, and artificial intelligence.

Background and Epidemiology

Brain metastases affect ~200,000 patients annually in the U.S. (10-fold more common than primary brain tumors). Incidence is rising with improved systemic therapies. The most frequent primary sites are lung (especially small-cell and non-small-cell), breast, melanoma, renal cell, colorectal, and others. Brain metastases portend poor prognosis (median survival historically 4–6 months with WBRT), but prognostic indices (e.g. RPA class, DS-GPA) stratify patients by factors like age, KPS, extracranial disease, and number of brain lesions. Management of brain metastases is multidisciplinary: neurosurgery (for large symptomatic lesions), SRS, WBRT, systemic therapy, and palliative care.

Radiobiology and Technical Aspects: WBRT typically delivers ~30–37.5 Gy in 10–15 fractions, aiming to sterilize visible and micrometastatic disease at the cost of diffuse brain dose. WBRT's biologic effect is fractionated, causing both tumor kill and diffuse injury to proliferating neural cells, especially the hippocampal neural progenitor niche (hence memory loss). In contrast, SRS delivers a high ablative dose (15–24 Gy) in one or a

few fractions to each lesion with steep dose fall-off. This spares normal brain, preserving neurocognition. SRS can be delivered via Gamma Knife, linac-based systems, or CyberKnife, with planning guided by high-resolution MRI. Modern techniques enable treating multiple lesions concurrently, and hypofractionated SRS (HFSRT) for larger tumors. Technical considerations include total tumor volume (which correlates with toxicity), lesion size/location (eloquent cortex, brainstem are challenging), and cumulative dose to normal brain. Hippocampal-avoidance WBRT (HA-WBRT) uses IMRT/VMAT to spare hippocampi (lowers memory deficits). Acute WBRT toxicities include alopecia, fatigue, headache, nausea; late effects include leukoencephalopathy, atrophy, cognitive decline, and radiation necrosis (in high-dose SRS).

Patient Selection Criteria: Selection balances extent of brain disease, systemic disease status, prognosis, and patient preferences. Historically, SRS was reserved for limited metastases (≤ 3 or 4) and WBRT for multiple. However, evidence has shifted this: ASTRO (2022) recommends SRS alone for 1–4 metastases (ECOG 0–2). For 5–10 metastases, SRS is “conditionally recommended” if total tumor volume is acceptable and life expectancy is adequate. NCCN 2024 similarly “favors” SRS over WBRT in limited disease. Key factors beyond number include *total tumor volume* (smaller volumes favor SRS), *tumor location* (deep/brainstem lesions may need fractionation or resection), *histology* (radioresistant tumors like melanoma or renal may need higher SRS doses), *molecular drivers* (e.g. EGFR/ALK in lung metastases may respond to TKIs), *age* (younger patients derive more from preserving cognition), and *extracranial control* (poor systemic disease may tilt toward WBRT or best supportive care). Age ranges vary; many trials include adult patients (median age ~55–65). Performance status (KPS/ECOG) is crucial: most studies enroll patients with KPS ≥ 70 –80. Until more data emerges for very high counts (>10–15 lesions), decisions for *numerous* metastases remain individualized. The ASTRO guideline notes that *number of metastases per se is becoming less crucial* and treatment choice should be individualized. For poor-prognosis patients, supportive care or short-course WBRT may be appropriate. After resection of a metastasis, postoperative SRS to the cavity is preferred over WBRT to preserve cognition.

METHODS

A comprehensive literature search (PubMed, Embase, Cochrane) was conducted for trials, meta-analyses, and guidelines through mid-2026 using terms such as “stereotactic radiosurgery”, “whole brain radiotherapy”, and “brain metastases”. Inclusion focused on comparative studies of SRS and WBRT (randomized or large cohort),

studies of neurocognitive/QoL outcomes, and international guidelines (ASTRO/ASCO/SNO, EANO, NCCN, ESMO). Key endpoints extracted included OS, intracranial progression, local/distant control, neurocognitive change (e.g. HVL-T-R, TMT-B scores), QoL scales (FACT-Br, EORTC QLQ-BN20), and toxicity rates. Evidence was graded qualitatively (level I–IV evidence) based on trial design and consistency. Tables were constructed summarizing pivotal trials and meta-analyses (see Tables 1–3). A mermaid-style timeline of major studies is provided (Figure 1). This review integrates high-quality evidence (RCTs, meta-analyses, guidelines) with key cohort studies for “multiple metastases” scenarios, recognizing that direct RCT data for >4 metastases are limited.

Efficacy Outcomes

Overall Survival

Overall survival (OS) for brain metastasis patients is driven largely by extracranial disease, but intracranial therapy can improve neurological outcomes. No high-level trial has shown an OS benefit from WBRT over SRS in multiple metastases. A recent meta-analysis of 35 studies (mostly observational) found that SRS was associated with a longer mean survival than WBRT (mean difference +4.38 months, 95% CI 3.10–6.57, $p<0.00001$). However, this difference was largely from retrospective data; two RCTs showed no significant OS difference between SRS and WBRT. For example, Brown et al. (JAMA 2016) randomized patients with 1–3 metastases to SRS alone vs. SRS+WBRT and found median OS 10.4 vs. 7.4 months (HR 1.02, $p=0.92$). Similarly, Yamamoto et al.’s multi-institutional cohort (Lancet Oncol 2014) reported no OS difference between patients with 2–4 vs. 5–10 metastases treated with SRS alone. Meta-analysis for very high metastatic burden shows somewhat worse OS for ≥ 10 lesions (pooled HR ≈ 1.10 vs. <10), but absolute survival remains comparable to systemic options. In practice, SRS is not expected to prolong survival beyond best systemic therapy, but it can improve neurological death rates by controlling brain disease.

For subgroups, younger patients and those with favorable prognostic indices (RPA Class I/II, high GPA scores)

derive more benefit from aggressive therapy. Histologies like small-cell lung or aggressive melanoma may require WBRT consideration if numerous lesions. Some data suggest slightly shorter median survival with higher lesion count even when treated with SRS: in one retrospective study, median OS was 8.1 mo for 2–4 lesions vs. 7.2 mo for 5–15 lesions ($p=0.001$). However, prognosis differences may reflect systemic disease status rather than cranial therapy. Overall, evidence to date indicates no OS inferiority of SRS-only strategies in patients with up to ~ 10 metastases, supporting SRS as a viable primary therapy.

Intracranial Control, Local and Distant Recurrences

Whole-brain RT maximizes control of micrometastatic disease, whereas SRS focuses on visible lesions. Thus, WBRT yields higher initial intracranial control but at the cost of cognitive side effects. In randomized trials, adding WBRT to SRS reduces new brain failures. For instance, in Brown 2016, intracranial PFS was longer with SRS+WBRT (HR for progression 3.6 favoring WBRT, $p<0.001$). However, improved control did not translate into OS benefit, and most recurrences after SRS alone can be salvaged.

Local control of treated lesions is excellent with both modalities (≈ 80 – 90% at 1 year with proper SRS dosing). Meta-analysis shows SRS improves lesion-level control compared to WBRT: local control risk ratio ~ 1.20 favoring SRS. Distant-brain control (new metastases outside treated sites) is worse with SRS alone (since WBRT would have treated them prophylactically). The NeurolSci meta found no significant difference in distant control (OR 0.61, $p=0.15$), though many such patients eventually develop new lesions. In practice, frequent MRI surveillance after SRS allows early salvage.

In multiple-mets cohorts, intracranial control is still adequate: e.g. the CYBER-SPACE trial (2025) reported 12-month freedom from WBRT (a surrogate for absence of extensive new disease) of $\sim 77\%$. Yamamoto et al. observed similar in-field control for 5–10 versus 2–4 lesions. Overall, SRS yields high local control but higher distant failure rates, whereas WBRT suppresses new lesions but at neurocognitive cost. Table 1 summarizes key trial outcomes.

Table 1: Selected Trials and Observational Studies (SRS vs WBRT)

Study (year)	Design / Patient N	Treatment Arms	Median OS (mo)	IC/PFS	Local Control	Cognitive/QoL outcomes	Source
Andrews et al. (JAMA 2004)	RCT, n=333	1–3 mets (RPA I–II)	WBRT (30 Gy) ± SRS (15–24 Gy)	6.5 (WBRT+SRS) vs 4.9 (WBRT) in single-lesion subgroup (p<0.05 for RPA I)	NR	SRS boost improved local control	Not reported (WW trial) [73†L139-L148]
Aoyama et al. (IJROBP 2006)	RCT, n=132	1–4 mets	SRS (±30 Gy WBRT)	~7–9 (no sig diff)	90% vs 60% (WBRT improved distant control)	1ly local vs ~80–90% (no diff)	Cognitive (MMSE) similar, trend favoring SRS alone [73†L149-L157]
Chang et al. (Lancet Oncol 2009)	RCT, n=60	1–3 mets	SRS vs. SRS+WBRT	Median OS 5.7 vs 6.0 (no diff)	No diff OS; WBRT better intracranial control	Local control high both arms	HVLT-R decline at 4mo: 52% (WBRT+SRS) vs 24% (SRS) [56†L210-L216] (cog); [73†L139-L148] (RTOG ref)
Brown et al. (JAMA 2016)	RCT, n=213	1–3 mets	SRS vs. SRS+WBRT (30 Gy/12fx)	10.4 vs 7.4 (HR 1.02; p=0.92)	Higher relapse after SRS alone (HR 3.6, p<0.001)	Local ~84% (both)	3-mo cognitive deterioration: 63.5% (SRS) vs 91.7% (WBRT+SRS); QoL better with SRS [75†L423-L432] (cog/QoL, QoLOS)
Yamamoto et al. (Lancet Oncol 2014)	Obs coh., n=1194	2–4 vs 5–10 mets	SRS alone	No sig diff OS (noninferior)	NR	~10.8 mo OS in both	Not reported (cohort) [64†L1-L4]
El Shafie et al. (Radiother Oncol 2026) CYBER-SPACE	RCT, n≈200	1–10 mets, no WBRT planned	SRS (monitor + repeat SRS)	Not given (trial ongoing)	12-mo WBRT-free: 77.1%	NR	Low neurologic death (10.1%), PFS not reported [30†L31-L39]
Meta-analysis (Mohamed et al. 2025)	Meta, 35 studies (27 obs + 8 RCT)	Brain mets (varied)	SRS vs WBRT	SRS gave +4.4 mo (obs), NS (RCTs)	Pooled HR_SRS > Pooled HR_WBRT	SRS local control better (RR 1.20)	SRS preserves cognition/QoL (presumed) [71†L87-L95][71†L99-L104]
Meta-analysis (Rozati et al. 2023)	Meta, n≈several	≥10 mets treated with SRS	SRS only (no WBRT group)	12-mo OS 20–40%; pooled HR (≥10 mets vs <10) 1.10 (p<0.01)	Not applicable	Not applicable	“Survival...acceptable; not deterrent to SRS” [70†L91-L100]

Abbreviations: HR = hazard ratio; IC = intracranial control; PFS = progression-free survival; OS = overall survival; QoL = quality of life.

Neurocognitive Outcomes

Cognitive decline is a key trade-off with cranial RT. WBRT causes diffuse injury to hippocampal stem cells and white matter, leading to declines in memory, executive function, and processing speed. By contrast, SRS spares most normal brain. Multiple trials confirm significantly less cognitive deterioration with SRS alone. In Chang et al., addition of WBRT to SRS *worsened* memory: 4-month decline in Hopkins Verbal Learning Test–Revised (HVLt-R) total recall occurred in 52% of WBRT+SRS patients versus only 24% with SRS alone. Brown et al. similarly found at 3 months a deterioration rate of 63.5% with SRS versus 91.7% with WBRT+SRS. These differences were statistically and clinically significant. For long-term survivors, cognitive deficits were still more common after WBRT (e.g. at 12 mo: 94.4% vs 60.0% decline).

In terms of specific tests, SRS patients score better on the HVLt-R (verbal learning/memory), Trail Making Test (executive function), and others. For example, in Brown

2016, the proportion with ≥ 1 standard deviation decline on HVLt-R delayed recall at 3 mo was 51.1% (WBRT+SRS) vs 19.7% (SRS alone) (OR ~ 3.4). Verbal fluency (COWAT) decline was 18.6% vs 1.9% ($p=0.01$). In each domain SRS was favored. The ASTRO guideline emphasizes preserving neurocognitive function.

Hippocampal-avoidance WBRT (HA-WBRT) plus memantine further mitigates decline compared to standard WBRT: NRG-CC001 (NEJM 2020) showed a 26% relative reduction in cognitive failure with HA-WBRT+memantine (adjusted HR 0.74, $p=0.03$). For example, at 6 months, delayed recall decline was 33.3% in WBRT+memantine vs 16.4% in HA-WBRT+memantine ($p=0.02$). Patients reported better memory and QoL with HA. Nonetheless, SRS alone yields the best preservation since no diffuse dose is given. In practice, validated neuropsychological batteries are recommended for monitoring (e.g. HVLt-R, TMT, COWAT, RBANS). Table 2 summarizes key cognitive outcomes.

Figure 1. Major Clinical Trials and Guideline Milestones in the Management of Brain Metastases (1990–2026)

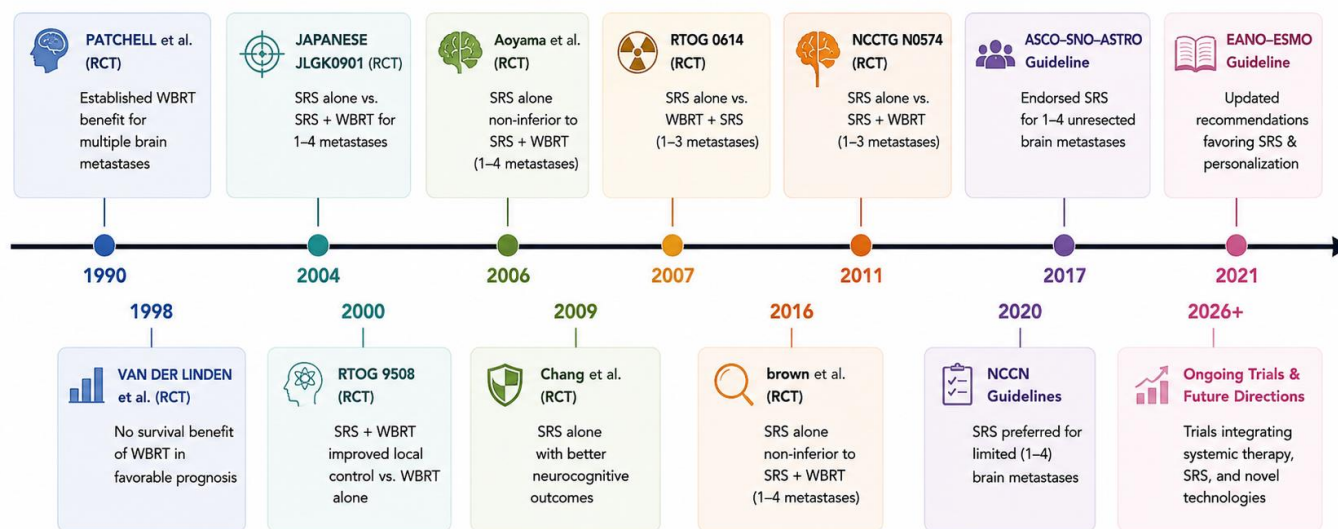


Figure 1. Major clinical trials and international guideline milestones that have shaped the management of patients with brain metastases from 1990 to 2026. The timeline illustrates the transition from routine whole-brain radiotherapy toward stereotactic radiosurgery–based personalized treatment strategies.

Quality of Life (QoL)

Quality of life is a critical endpoint for brain metastasis patients. Validated instruments include FACT-Br (Functional Assessment of Cancer Therapy – Brain), EORTC QLQ-BN20 (brain tumor module), and EQ-5D. In Brown et al., SRS alone showed better QoL preservation: at 3 months, the FACT-Br overall score declined by a mean of -1.3 points with SRS vs -10.9 with

WBRT+SRS (mean difference 9.6 points, $p=0.002$). Domains such as physical, functional, and brain-specific QoL also favored SRS. Similarly, in NRG-CC001, HA-WBRT+memantine patients reported fewer cognitive symptoms and better QLQ-C30 scores than WBRT patients. Multiple studies report that cognitive preservation with SRS translates into better daily functioning and independence. In practice, routine QoL

assessment is encouraged (e.g. EQ-5D at each visit). Overall, these data reinforce that SRS-based approaches maintain QoL and neurocognitive function better than WBRT, even when intracranial control is similar.

Adverse Events and Toxicity

SRS Toxicity: Generally well tolerated. Common acute effects include headache and nausea (due to edema) managed with steroids. Serious late toxicity is radiation necrosis (RN), which can occur months after high-dose SRS. RN rates vary; larger lesions and higher doses increase risk (reported 5–25% in various series). Symptoms of RN include focal deficits or seizures, treated with corticosteroids or bevacizumab; rarely surgical resection is needed. Long-term, SRS to multiple lesions can cause scattered microvascular changes, but overall diffuse cognitive effects are minimal.

WBRT Toxicity: Acute WBRT causes fatigue, alopecia, skin erythema, and cognitive foggy. Subacute “CRCE” (acute brain swelling) occurs in a minority. The hallmark late effect is neurocognitive decline (“brain radiotherapy encephalopathy”) manifested as memory loss, attention deficits, and leukoencephalopathy, as discussed above. These can significantly impair life quality and daily activities. Brain atrophy and white-matter changes are often seen on MRI. Other late effects (<10%) include endocrine dysfunction (hypothyroidism/pituitary) and hearing loss if cochleae are irradiated. The addition of memantine reduces but does not abolish cognitive sequelae.

ASTRO guidelines highlight toxicity differences: routine adjuvant WBRT is not recommended after SRS or surgery for limited metastases due to lack of survival benefit and risk of neurotoxicity. HA-WBRT is specifically recommended when WBRT is used to “preserve memory function”. Steroid use should be minimized to avoid cognitive and systemic side effects.

For both modalities, neurological adverse events (e.g. seizures, hemorrhage) are monitored. Table 2 lists common toxicities.

Salvage Therapies

When intracranial progression occurs after initial therapy, further local treatment may be pursued. After SRS alone, new metastases are often managed with additional SRS (“salvage SRS”) as long as cumulative normal brain dose allows. The CYBER-SPACE trial protocol exemplified this: patients with new lesions continued iterative SRS, resulting in only ~23% requiring eventual WBRT by 1 year. Several case series support multiple courses of SRS for new lesions. This strategy can prolong intracranial control with preserved cognition.

After WBRT, salvage SRS to isolated recurrences or metastases is feasible. EANO guidelines note that “salvage SRS following initial WBRT can be an option

for local control and survival” (Level C). Surgery may be considered for large solitary recurrences. Systemic therapies (targeted agents or immunotherapy) also play a salvage role, sometimes obviating RT.

In sum, salvage therapy selection is individualized: SRS is often repeated or added in lieu of WBRT if possible; WBRT is reserved for widespread or intractable CNS recurrence. This flexibility allows deferring WBRT and its cognitive cost while maintaining control.

Cost-Effectiveness

Economic analyses generally find WBRT is less costly per treatment, but SRS offers better quality-adjusted life years (QALYs) in suitable patients. One cost-utility model found mean treatment costs (including salvage) of ~\$18.6K for SRS alone vs ~\$9.6K for WBRT. The incremental cost-effectiveness ratio favored SRS in single-lesion cases. Another analysis reported per-life-year costs (2–4 metastases): \$66K (SRS) vs \$34K (WBRT). WBRT for >4 metastases remained ~\$34K/LY. However, these older models did not fully account for memantine/HA-WBRT costs or long-term cognitive QALYs. Contemporary assessments (with memantine) are needed. In practice, SRS is more resource-intensive (special equipment, planning), but preserves neurocognition, which has intangible value. Several reviews conclude that SRS (alone or with systemic therapy) is cost-effective for limited metastases in patients with good performance status, whereas routine WBRT for all carries hidden “neurocosts.”

Guidelines and Consensus Statements

The evolving evidence has been incorporated into recent guidelines:

- **ASTRO/ASCO/SNO (2021–22):** For 1–4 metastases (ECOG 0–2), SRS alone is recommended. For 5–10 metastases, SRS is *conditionally recommended*, emphasizing patient-specific factors. Adjuvant WBRT is *not* routinely recommended after SRS or resection for limited disease. For extensive brain mets or poor prognosis, WBRT (±memantine and hippocampal avoidance) may be used; memantine and HA-WBRT are **strongly recommended** when WBRT is given. Notably, guidelines stress decision-making should consider total tumor volume, location, age, and systemic status, not just lesion count. For resected cavities, post-op SRS is preferred over WBRT.
- **EANO/ESMO (2021–22):** Similarly advise against routine WBRT post-SRS/resection for limited metastases (Level A). For multiple metastases, treatment is individualized; EANO notes increasing acceptance of SRS, and states that the **absolute number of lesions** is less crucial than clinical context. Salvage SRS for new mets is endorsed (Level C).

- **NCCN (2024 CNS Cancers):** Recommends SRS alone for limited brain mets when feasible, reflecting accumulated evidence. WBRT (preferably hippocampal-sparing with memantine) is reserved for diffuse or uncontrolled cases. NCCN also highlights the role of systemic therapy for certain subtypes (e.g. TKIs for EGFR/ALK lung mets, immunotherapy for melanoma) in CNS disease.

Consensus across societies is clear: **use WBRT less frequently**. Table 3 summarizes key recommendations. These guidelines rely on systematic evidence reviews (ASTRO reviewed data through 2020) and emphasize neurocognitive outcomes.

Clinical Implications

Recent evidence supports stereotactic radiosurgery as the preferred treatment modality for carefully selected patients with multiple brain metastases. Clinical decision-making should consider total tumor volume, patient performance status, molecular subtype, expected survival, and patient preferences rather than relying solely on the number of intracranial lesions. Preservation of neurocognitive function and quality of life has become a major therapeutic objective, making SRS the preferred option whenever technically feasible. Whole-brain radiotherapy remains appropriate for patients with diffuse intracranial disease, leptomeningeal dissemination, poor performance status, or when repeated stereotactic treatment is not feasible.

Ongoing Trials and Future Directions

Several trials are addressing knowledge gaps:

- **SRS in >4–10 metastases:** Trials are ongoing to provide RCT evidence. NRG BN003 (US) is a phase III trial randomizing patients with 4–15 brain mets to SRS versus HA-WBRT with memantine, with cognitive decline as the primary endpoint. A Japanese study (JCOG1906) is testing SRS vs HA-WBRT for 5–15 mets. Preliminary data from single-arm studies and the CYBER-SPACE trial support SRS, but definitive phase III results are awaited.
- **Hippocampal-Avoidance WBRT:** NRG-CC001 (published) already showed HA-WBRT+memantine significantly reduces cognitive failure risk (HR 0.74). Follow-ups and broader adoption are ongoing. Novel neuroprotective strategies (radical sparing of other brain substructures, N-methyl-D-aspartate antagonists, anti-inflammatories) are under investigation.
- **Systemic Therapies + RT:** Targeted therapies (e.g. osimertinib, alectinib) and checkpoint inhibitors have intracranial efficacy. Current research explores sequencing/combining these agents with SRS/WBRT. For example, trials are examining whether SRS plus PD-1

inhibitors improve outcomes in melanoma or lung brain mets. Immunotherapy may enhance radiosurgery effects (abscopal phenomena) but also raise RN risk. Optimal timing (concurrent vs sequential) is under study.

- **“Neurocognitive rescue” strategies:** Trials of cognition-enhancing drugs (memantine, donepezil) or rehabilitative interventions alongside RT continue. The NRG-CC004 trial is studying memantine in patients receiving SRS to multiple mets.
- **SRS Technology:** Research into fractionation schemes (e.g. 3–5 fractions for larger tumors), novel delivery (proton SRS, MR-guided RT), and AI-driven planning will refine SRS safety.

In summary, the paradigm is shifting towards personalized therapy: SRS and systemic agents for most patients, WBRT selectively. Future evidence will refine thresholds (number/volume cut-offs), combination strategies, and long-term neuroprotection measures.

Practical Clinical Recommendations and Research Gaps

Recommendations: For patients with multiple brain metastases and reasonable prognoses, **consider SRS-based approaches** whenever feasible. Specifically:

- **1–4 lesions:** SRS alone (single or few fractions) is standard. WBRT is discouraged as primary or adjuvant therapy.
- **5–10 lesions:** SRS is reasonable if total volume is limited and patient is fit. Multidisciplinary discussion is essential; factors like tumor biology, systemic options, and patient preference guide therapy.
- **>10 lesions:** Historically WBRT was used, but SRS (possibly staged over time) can be considered in selected cases with excellent systemic control. If WBRT is given, use hippocampal avoidance and memantine (until more evidence for SRS emerges).
- **Post-resection:** SRS to the cavity is preferred over WBRT.
- **Neurological monitoring:** Obtain baseline and periodic neurocognitive assessments (e.g. every 3–6 months) for early detection of decline.
- **Surveillance:** Use frequent MRI follow-up (e.g. q3 months first year) to detect new lesions early, enabling salvage SRS.
- **Systemic therapy integration:** For EGFR/ALK+ lung or BRAF+ melanoma CNS mets, consider targeted agents that can obviate or delay radiation; integrate immunotherapy as appropriate.
- **Palliation:** In poor performance patients, WBRT may provide symptom relief, but best supportive care and steroids should be considered given limited OS improvement.

Limitations

Although this review summarizes the best available evidence, several limitations should be acknowledged. Most comparative studies evaluating stereotactic radiosurgery in patients with numerous brain metastases are retrospective or observational, introducing potential selection bias. High-quality randomized controlled trials involving patients with more than ten brain metastases remain limited. Considerable heterogeneity exists among studies regarding patient selection, treatment techniques, radiation doses, systemic therapies, neurocognitive assessment methods, and follow-up duration. Furthermore, long-term cognitive outcomes beyond two years remain insufficiently reported, particularly in the era of modern targeted therapies and immunotherapy. Therefore, interpretation of current evidence should consider these limitations.

Research Gaps

The critical need is high-level evidence for multiple (>4) metastases. We await results of ongoing phase III trials (e.g. NRG BN003, JCOG1906). Long-term cognitive outcomes beyond 1–2 years are underreported, especially in conjunction with new systemic therapies. Optimal SRS dose/fractionation for large combined tumor volumes remains to be defined. The interplay of immunotherapy with cranial RT (radiosensitization vs toxicity) needs elucidation in trials. Cost-effectiveness analyses should be updated to include hippocampal-sparing techniques and novel drugs. Biomarkers to predict RN versus recurrence (imaging or serum) are also an area of active research.

Future Perspectives

Future management of brain metastases will increasingly focus on precision medicine and personalized radiation oncology. Artificial intelligence-assisted treatment planning, radiomics-based prediction models, MR-guided adaptive radiotherapy, proton stereotactic radiosurgery, and genomic biomarkers are expected to optimize patient selection and treatment outcomes. Integration of stereotactic radiosurgery with immunotherapy and molecular targeted therapies may further improve intracranial disease control while minimizing treatment-related toxicity. Large multicenter randomized trials are required to establish the optimal management of patients with extensive brain metastases and to define evidence-based treatment algorithms.

Key Clinical Practice Points

- SRS should be considered the preferred treatment for patients with limited cumulative intracranial tumor volume.
- WBRT should be reserved for patients with diffuse metastatic disease or poor prognostic features.

- Hippocampal-avoidance WBRT with memantine should be used whenever WBRT is indicated.
- Routine MRI surveillance following SRS is essential for early detection of new brain metastases.
- Multidisciplinary decision-making remains fundamental for optimizing patient outcomes.

CONCLUSION

For patients with multiple brain metastases, stereotactic radiosurgery – alone or as part of a multimodal approach – is increasingly validated as a safe, effective alternative to whole-brain radiotherapy. It achieves durable local control with minimal cognitive decline, at the cost of more frequent salvage treatments. Guideline-endorsed patient selection (good KPS, controlled extracranial disease) ensures benefits outweigh risks. Current evidence supports tailoring therapy to individual factors beyond lesion count, favoring brain-sparing treatments whenever possible. Clinicians should incorporate patient values (cognition, quality of life) into the decision. Ongoing trials will clarify the upper limits of SRS candidacy and refine combined modality care. Overall, a move toward SRS-centric management promises improved patient-centered outcomes, but judicious use of WBRT (with neuroprotective measures) remains warranted for widespread disease or poor-prognosis cases.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this review article.

FUNDING

The authors received no financial support or external funding for the preparation of this manuscript.

AUTHOR CONTRIBUTIONS

Dr. Nabin Kumar Yadav: Conceptualization, literature search, manuscript preparation, critical revision, and final approval.

Yunusov Umrbek Odilovich: Literature review, data collection, interpretation of evidence, manuscript editing.

Jaxonov Mirzohid Mustaqimovich: Scientific review, critical revision, supervision, and final approval of the manuscript.

DATA AVAILABILITY

No new datasets were generated or analyzed during the preparation of this review article.

ETHICS STATEMENT

Ethical approval and informed consent were not required because this study is a narrative review based entirely on previously published literature.

ACKNOWLEDGEMENTS

The authors sincerely acknowledge all researchers and clinicians whose published work contributed to the preparation of this review article.

Abbreviation	Meaning
SRS	Stereotactic Radiosurgery
WBRT	Whole Brain Radiotherapy
OS	Overall Survival
QoL	Quality of Life
KPS	Karnofsky Performance Status
MRI	Magnetic Resonance Imaging

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