



The Relationship between Radiotherapy and Cognitive Impairment in Brain Tumor Patients : A Systematic Review

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ABSTRACT

Introduction: Radiotherapy (RT) is a cornerstone in treating brain tumors but is associated with potential cognitive decline. The relationship between RT and cognitive impairment is complex, influenced by tumor type, RT modality, and patient-specific factors.

Methods: This systematic review synthesized data from 80 included studies encompassing a broad range of designs, from randomized controlled trials, etc. We extracted data on patient populations, RT details (whole-brain radiotherapy [WBRT], stereotactic radiosurgery [SRS], proton therapy), cognitive assessment methods, outcomes, dose-response relationships, underlying mechanisms, risk factors, and prevention strategies.

Results: WBRT produced the most severe cognitive decline, with 91.7% of patients experiencing deterioration at 3 months

compared to 63.5% with SRS alone (P. Brown et al., 2016). SRS-based approaches resulted in substantially less cognitive morbidity. Hippocampal-avoidance (HA)-WBRT significantly reduced cognitive failure (adjusted HR=0.74, p=0.016) (Crockett & Simões, 2023). Mean brain dose inversely predicted cognitive trajectories in IDH-mutant glioma (Jaspers et al., 2024). Key mechanisms include vascular injury, white matter damage, neuroinflammation, and oxidative stress. Risk factors include older age, low cognitive reserve, and pre-existing leukoencephalopathy.

Discussion: The findings reveal a consistent hierarchy of cognitive toxicity: WBRT > SRS > focal/partial brain RT. A central tension exists between maximizing tumor control (achieved by WBRT) and preserving cognition (achieved by SRS and hippocampal sparing). Distinguishing tumor-related from treatment-related cognitive effects remains a key challenge, as baseline impairment is highly prevalent. Dose-response relationships are structure-specific, implicating the hippocampus, entorhinal cortex, thalamus, and white matter tracts. Neuroprotective strategies, including memantine and HA-WBRT, show benefit, while donepezil offers modest improvements.

Conclusion: Modern RT protocols should prioritize cognitive preservation through appropriate modality selection (SRS alone for 1-3 metastases), hippocampal avoidance, and minimizing mean brain dose. Future research should focus on integrating cognitive endpoints into clinical trial design and validating dosimetric constraints for distributed brain structures.

Keywords: Radiotherapy, cognitive impairment, brain tumors, whole-brain radiotherapy, stereotactic radiosurgery, hippocampal avoidance, neuroprotection.

INTRODUCTION

Background

Radiotherapy (RT) is an essential treatment modality for both primary and metastatic brain tumors, significantly improving local control and, in some cases, overall survival (P. Brown et al., 2016). However, the therapeutic benefits of cranial RT are frequently offset by significant neurocognitive toxicity (Tallet et al., 2012). Patients often experience declines in memory, executive function, processing speed, and attention, which can severely impact quality of life and functional independence (Salans et al., 2020). The spectrum of cognitive dysfunction ranges from mild impairment to dementia-level disability, with a high prevalence of 66% of post-irradiation survivors meeting criteria for mild cognitive impairment (Cramer et al., 2018). The advent of sophisticated RT techniques, including stereotactic radiosurgery (SRS), intensity-modulated RT (IMRT), and proton beam therapy, has introduced variability in cognitive outcomes, yet a systematic and comparative synthesis of these effects is necessary (Lehrer et al., 2019; Van Grinsven et al., 2021).

Research Gap

Despite a large and growing body of literature, significant gaps remain. First, many studies fail to adequately separate the cognitive effects of the tumor itself from those of the treatment, given that up to 91% of patients with brain metastases already demonstrate baseline cognitive impairment prior to any intervention (Van Grinsven et al., 2021). Second, the specific dose-response relationships for distinct brain structures—such as the hippocampus, entorhinal cortex, thalamus, and white matter tracts—are still being defined, limiting the ability to establish evidence-based organ-at-risk constraints (Yu et al., 2021; Gudipati et al., 2022). Third, while hippocampal avoidance (HA) has shown promise, its integration with pharmacological neuroprotectants like memantine requires further elucidation (Crockett & Simões, 2023). Fourth, the long-term cognitive trajectory of patients with low-grade gliomas (LGG) versus high-grade gliomas (HGG) or

metastases differs substantially, yet comparative analyses across these populations are scarce (Laack et al., 2005; Jaspers et al., 2025).

Novelty

This systematic review offers a novel, comprehensive synthesis by explicitly comparing cognitive outcomes across the full range of RT modalities—from WBRT to SRS to advanced proton therapy—within a unified framework. Unlike prior meta-analyses that focused on a single modality or tumor type, this review integrates data on dose-structure-cognition specificity, biological mechanisms (vascular injury, neuroinflammation, oxidative stress), and modifiable risk factors (age, cognitive reserve, pre-existing leukoencephalopathy). Furthermore, it critically evaluates emerging neuroprotective strategies, including hippocampal sparing, memantine, donepezil, and the novel superoxide dismutase mimetic BMX-001, providing a current and clinically actionable evidence base (Kirkpatrick et al., 2020; Peters et al., 2022).

Objectives

The primary objective of this systematic review is to synthesize and critically appraise the evidence regarding the relationship between radiotherapy and cognitive impairment in adult brain tumor patients. Specifically, this review aims to: (1) quantify the incidence and severity of cognitive decline across different RT modalities; (2) identify dose-response relationships and critical brain structures mediating specific cognitive domains; (3) elucidate the biological mechanisms underlying radiation-induced cognitive dysfunction; (4) characterize patient- and treatment-related risk factors; and (5) evaluate the efficacy of existing prevention and mitigation strategies.

Hypothesis

We hypothesized that (1) WBRT would be associated with the most severe and prevalent cognitive decline, particularly in memory and processing speed; (2) SRS and partial brain RT would preserve cognitive function relative to WBRT; (3) hippocampal avoidance would significantly attenuate cognitive decline without compromising tumor control; and (4) mean brain dose would independently predict cognitive trajectories, even in populations with stable group-level performance.

Benefits of the Study

The benefits of this study are multifold. For clinicians, it provides a clear, evidence-based hierarchy of cognitive toxicity to guide modality selection and patient counseling. For radiation oncologists, it offers specific dose constraints for critical brain structures (e.g., hippocampus $D_{max} \leq 8.4$ Gy for SRS, white matter tract $D_{max} \leq 12$ Gy). For patients, it clarifies the trade-off between tumor control and cognitive preservation, enabling shared decision-making. For researchers, it identifies knowledge gaps and establishes a framework for future trials integrating cognitive endpoints and advanced neuroimaging.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate The Relationship between Radiotherapy and Cognitive Impairment in Brain Tumor Patients.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population - Brain Tumor Patients:** Does the study involve patients diagnosed with primary or metastatic brain tumors?
- **Population - Adult Patients:** Does the study focus on adult patients (18 years or older), or if it includes mixed age groups, are pediatric patients (under 18 years) either excluded or separately analyzable?
- **Intervention - Radiotherapy:** Does the study examine radiotherapy as a treatment modality (including whole brain radiotherapy, stereotactic radiosurgery, or fractionated stereotactic radiotherapy)?

- **Outcome - Cognitive Assessment:** Does the study assess cognitive function using validated neuropsychological tests, cognitive screening tools, or patient-reported cognitive outcomes?
- **Temporal Assessment:** Does the study evaluate cognitive function either before and after radiotherapy, or compare cognitive function between irradiated and non-irradiated patients?
- **Study Design:** Is the study design a randomized controlled trial, etc ?
- **Radiotherapy Component:** Does the study include a radiotherapy component (i.e., is it NOT examining only chemotherapy or surgical interventions without any radiotherapy)?
- **Separable Brain Tumor Population:** Can brain tumor patients be identified and analyzed separately from other cancer populations in this study, or does the study focus exclusively on brain tumor patients?
- **Adequate Study Type and Sample Size:** Is this study NOT a case report, case series with fewer than 10 patients, editorial, letter, or conference abstract?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Brain Tumor	Radiotherapy	SRS vs. WBRT	Cognitive Impairment
Keyword 2	Brain Metastases	Whole Brain Radiotherapy (WBRT)	Hippocampal Avoidance	Neurocognitive Decline
Keyword 3	Primary Brain Tumor	Stereotactic Radiosurgery (SRS)	High-dose vs. Low-dose	Memory Dysfunction

Keyword	Adult Patients	Fractionated Radiotherapy	Photon vs. Proton	Quality of Life (QOL)
4				

The Boolean MeSH keywords inputted on databases for this research are: (*"Brain Tumor" OR "Brain Metastases" OR "Primary Brain Tumor" OR "Adult Patients"*) AND (*"Radiotherapy" OR "Whole Brain Radiotherapy" OR "Stereotactic Radiosurgery" OR "Fractionated Radiotherapy"*) AND (*"SRS vs. WBRT" OR "Hippocampal Avoidance" OR "High-dose vs. Low-dose" OR "Photon vs. Proton"*) AND (*"Cognitive Impairment" OR "Neurocognitive Decline" OR "Memory Dysfunction" OR "Quality of Life"*)

Data extraction

- **Patient Population:**

Extract characteristics of brain tumor patients who received radiotherapy, including:

- Primary brain tumor type and grade OR brain metastases from specific primary sites
- Sample size for cognitive analysis
- Age range and mean age
- Time since tumor diagnosis
- Prior treatments (surgery, chemotherapy) before radiotherapy
- Baseline cognitive status if reported

- **Radiotherapy Details:**

Extract specific radiotherapy parameters that could influence cognitive outcomes:

- Total dose (Gy) and fractionation schedule
- Radiotherapy technique (whole brain, partial brain, stereotactic, etc.)
- Brain regions/volumes irradiated and dose distribution

- Use of hippocampal sparing or other neuroprotective techniques
- Concurrent treatments during radiotherapy

- **Cognitive Assessment:**

Extract methods used to evaluate cognitive function in brain tumor patients receiving radiotherapy:

- Specific neuropsychological tests or cognitive batteries used
- Cognitive domains assessed (memory, attention, executive function, processing speed, etc.)
- Assessment timing relative to radiotherapy (baseline, during treatment, follow-up intervals)
- Duration of cognitive follow-up
- Whether assessments controlled for tumor effects vs. treatment effects

- **Cognitive Outcomes:**

Extract findings on cognitive dysfunction in brain tumor patients after radiotherapy:

- Specific cognitive domains affected and severity of impairment
- Prevalence/incidence of cognitive dysfunction
- Quantitative measures of cognitive decline (effect sizes, mean differences, percentages)
- Comparison to baseline or control groups
- Functional impact on quality of life or daily activities

- **Timeline Effects:**

Extract temporal patterns of cognitive dysfunction following brain radiotherapy:

- Acute effects (during or immediately after treatment)
- Early delayed effects (weeks to months)
- Late delayed effects (months to years)
- Progressive vs. stable cognitive changes over time
- Recovery patterns if observed
- Time to onset of cognitive symptoms

- **Dose-Response Relationships:**

Extract evidence for dose-dependent cognitive effects in brain tumor patients:

- Threshold doses associated with cognitive dysfunction
- Correlation between radiation dose to specific brain regions and cognitive outcomes
- Volume effects (relationship between irradiated brain volume and cognitive impact)
- Comparison of different dose/fractionation schemes
- Critical brain structures where dose correlates with cognitive function

- **Underlying Mechanisms:**

Extract biological mechanisms proposed or demonstrated for radiotherapy-induced cognitive dysfunction:

- Neuroinflammation markers and pathways

- Vascular changes (blood flow, blood-brain barrier disruption)
- White matter changes or demyelination
- Neuronal loss or synaptic dysfunction
- Metabolic changes in brain tissue
- Molecular pathways involved (oxidative stress, protein misfolding, etc.)

- **Risk Factors:**

Extract patient and treatment factors that modify cognitive risk from brain radiotherapy:

- Age-related vulnerability (pediatric vs. adult vs. elderly)
- Tumor location effects on cognitive outcomes
- Baseline cognitive reserve or education level
- Genetic factors influencing radiosensitivity
- Concurrent medications or comorbidities
- Gender differences in cognitive susceptibility

- **Prevention Strategies:**

Extract interventions tested to prevent or reduce cognitive dysfunction from brain radiotherapy:

- Radioprotective agents (memantine, donepezil, etc.) with dosing and timing
- Modified radiotherapy techniques (hippocampal sparing, proton therapy)
- Cognitive training or rehabilitation programs

- Pharmacological interventions during or after radiotherapy
- Lifestyle interventions (exercise, diet)
- Efficacy outcomes and optimal timing of interventions

- **Study Methodology:**

Extract key methodological aspects relevant to interpreting cognitive-radiotherapy relationships:

- Study design (RCT, etc.)
- Presence and characteristics of control groups
- Methods for separating tumor effects from treatment effects
- Neuroimaging techniques used (MRI, PET, fMRI) and findings
- Statistical approaches for analyzing dose-response relationships
- Potential confounders addressed or limitations acknowledged

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Brain Tumor" OR "Brain Metastases" OR "Primary Brain Tumor" OR "Adult Patients") AND ("Radiotherapy" OR "Whole Brain Radiotherapy" OR "Stereotactic Radiosurgery" OR "Fractionated Radiotherapy") AND ("SRS vs. WBRT" OR "Hippocampal Avoidance" OR "High-dose vs. Low-dose" OR "Photon vs. Proton") AND ("Cognitive Impairment" OR "Neurocognitive Decline" OR "Memory Dysfunction" OR "Quality of Life")	63
Semantic Scholar	("Brain Tumor" OR "Brain Metastases" OR "Primary Brain Tumor" OR "Adult Patients") AND ("Radiotherapy" OR "Whole Brain Radiotherapy" OR "Stereotactic Radiosurgery" OR "Fractionated Radiotherapy") AND ("SRS vs. WBRT" OR "Hippocampal Avoidance" OR "High-dose vs. Low-dose" OR "Photon vs. Proton") AND ("Cognitive Impairment" OR "Neurocognitive Decline" OR "Memory Dysfunction" OR "Quality of Life")	250
Springer	("Brain Tumor" OR "Brain Metastases" OR "Primary Brain Tumor" OR "Adult Patients") AND ("Radiotherapy" OR "Whole Brain Radiotherapy" OR "Stereotactic Radiosurgery" OR "Fractionated Radiotherapy") AND ("SRS vs. WBRT" OR "Hippocampal Avoidance" OR "High-dose vs. Low-dose" OR "Photon vs. Proton") AND ("Cognitive Impairment" OR "Neurocognitive Decline" OR "Memory Dysfunction" OR "Quality of Life")	277
Google Scholar	("Brain Tumor" OR "Brain Metastases" OR "Primary Brain Tumor" OR "Adult Patients") AND ("Radiotherapy" OR "Whole Brain Radiotherapy" OR "Stereotactic Radiosurgery" OR "Fractionated Radiotherapy") AND ("SRS vs. WBRT" OR "Hippocampal Avoidance" OR "High-dose vs. Low-dose" OR "Photon vs. Proton") AND ("Cognitive Impairment" OR "Neurocognitive Decline" OR "Memory Dysfunction" OR "Quality of Life")	872
Wiley Online Library	("Brain Tumor" OR "Brain Metastases" OR "Primary Brain Tumor" OR "Adult Patients") AND ("Radiotherapy" OR "Whole Brain Radiotherapy" OR "Stereotactic Radiosurgery" OR "Fractionated Radiotherapy") AND ("SRS vs. WBRT" OR "Hippocampal Avoidance" OR "High-dose vs. Low-dose" OR "Photon vs. Proton") AND ("Cognitive Impairment" OR "Neurocognitive Decline" OR "Memory Dysfunction" OR "Quality of Life")	101

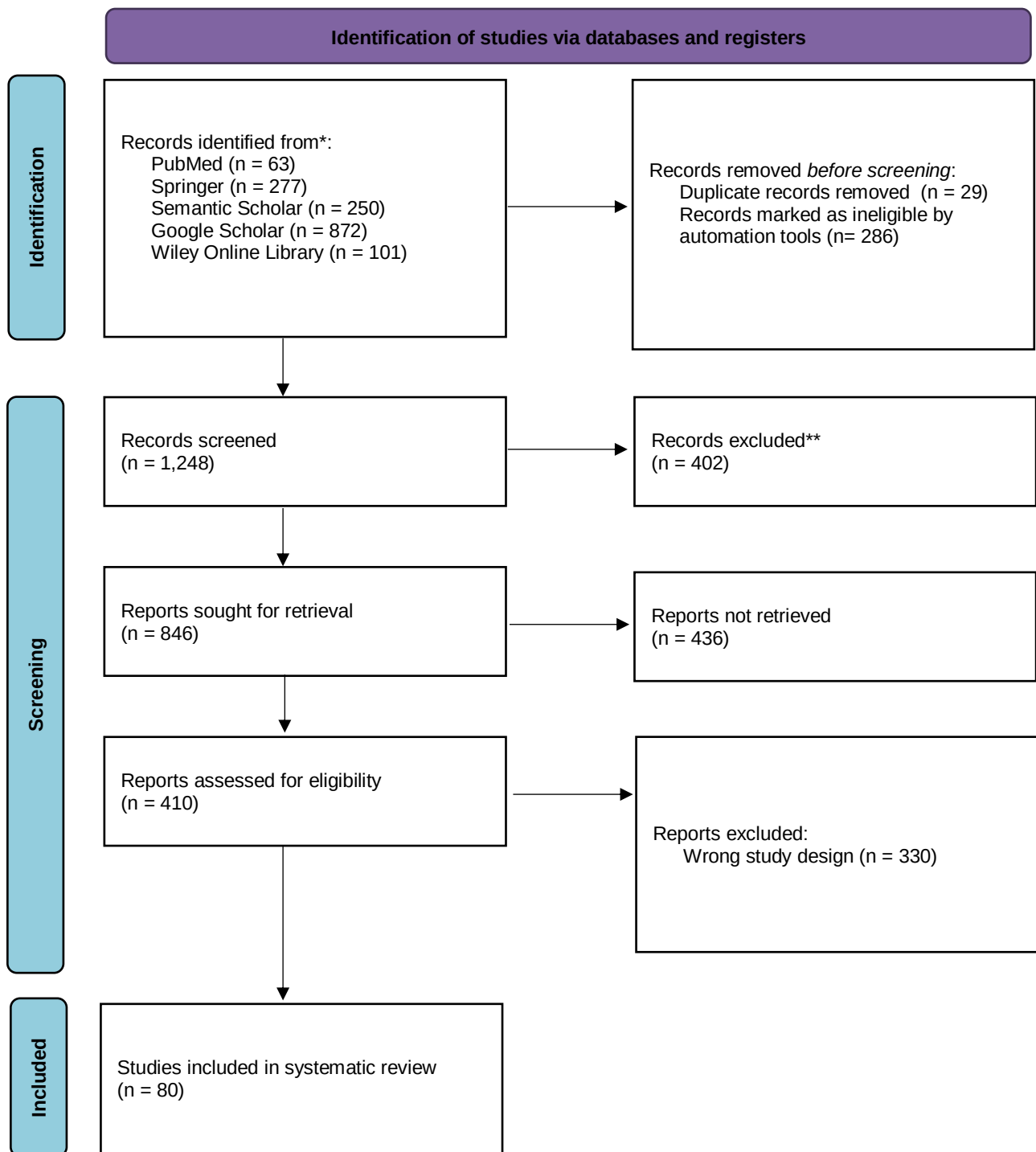


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
P. Brown et al., 2016 [1]	Low	Low	Low	Low	Low	Low
C. Armstrong et al., 2012 [25]	Low	Moderate	Low	Moderate	Low	Moderate
E. V. van Grinsven et al., 2021 [4]	Low	Low	Low	Moderate	Low	Moderate
J. Palmer et al., 2022 [26]	Low	Low	Low	Low	Low	Low
S. Gudipati et al., 2022 [11]	Moderate	Moderate	Low	Moderate	Low	Moderate
M. Salans et al., 2020 [27]	Moderate	Moderate	Low	Moderate	Low	Moderate
W. Schimmel et al., 2022 [28]	Low	Low	Low	Moderate	Low	Moderate
K. Redmond et al., 2015 [29]	Low	Moderate	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
F. Yang et al., 2022 [9]	Low	Low	Low	Low	Low	Low
J. Yu et al., 2021 [12]	Moderate	Moderate	Low	Moderate	Low	Moderate
Connor Puett et al., 2025 [14]	Low	Low	Low	Low	Low	Low
D. M. J. Pelak et al., 2025 [24]	Low	Low	Low	Moderate	Low	Low
E. Lehrer et al., 2019 [2]	Low	Low	Low	Low	Low	Low
J. Kirkpatrick et al., 2020 [30]	Low	Moderate	Unclear	Moderate	Low	Moderate
C. Hahn et al., 2005 [31]	Moderate	Moderate	Low	High	Moderate	High
T. Lawrie et al., 2019 [32]	Low	Low	Low	Low	Low	Low
R. Farjam et al., 2015 [10]	Low	Moderate	Low	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
N. Laack et al., 2005 [5]	Low	Moderate	Low	Moderate	Low	Moderate
J. Jaspers et al., 2025 [6]	Low	Low	Low	Low	Low	Low
Jianpeng Ma et al., 2024 [33]	Moderate	Moderate	Low	Moderate	Low	Moderate
H. Aoyama et al., 2007 [34]	Low	Moderate	Low	Moderate	Low	Moderate
A. Tallet et al., 2012 [3]	Low	Low	Low	Low	Low	Low
S. Rapp et al., 2015 [17]	Low	Low	Low	Low	Low	Low
T. Armstrong et al., 2013 [35]	Low	Low	Low	Moderate	Low	Low
Ansa Maer Cole et al., 2013 [36]	Moderate	Moderate	Low	Moderate	Low	Moderate
P. Brown et al., 2021 [22]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
B. Fisher et al., 2005 [37]	Moderate	Moderate	Low	High	Moderate	High
J. Butler et al., 2007 [38]	Low	Low	Low	Moderate	Low	Low
C. Koutsarnakis et al., 2021 [39]	Low	Low	Low	Low	Low	Low
Nicholas F. Marko & R. Weil, 2010 [40]	Unclear	Unclear	Unclear	Unclear	Low	Unclear
C. Crockett & R. Simões, 2023 [20]	Low	Low	Low	Low	Low	Low
M. Naughton et al., 2010 [41]	Moderate	Moderate	Low	Moderate	Low	Moderate
M. van der Meulen et al., 2021 [42]	Low	Low	Low	Low	Low	Low
M. Tibbs et al., 2019 [18]	Low	Moderate	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Julia R. Schneider et al., 2017 [43]	Low	Low	Low	Low	Low	Low
N. Chiannikulchai et al., 2016 [44]	Moderate	High	Moderate	Moderate	Moderate	High
G. Puglisi et al., 2025 [19]	Low	Low	Low	Low	Low	Low
L. Kępka et al., 2016 [45]	Low	Low	Low	Moderate	Low	Low
A. Rydelius et al., 2020 [7]	Low	Moderate	Low	Moderate	Low	Moderate
A. Tooze & J. Sheehan, 2018 [46]	Moderate	Moderate	Low	Moderate	Low	Moderate
B. Page et al., 2015 [47]	Low	Low	Low	Moderate	Low	Low
S. Hardy et al., 2020 [48]	Low	Moderate	Low	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
R. Prabhu et al., 2014 [49]	Low	Low	Low	Moderate	Low	Low
J. Jaspers et al., 2024 [8]	Low	Low	Low	Low	Low	Low
S. Hardy et al., 2023 [50]	Low	Moderate	Low	Moderate	Low	Moderate
Tarek Bou Dargham et al., 2025 [51]	Low	Low	Low	Low	Low	Low
M. Salans et al., 2021 [52]	Moderate	Moderate	Low	Moderate	Low	Moderate
Prerana Baruah et al., 2025 [53]	Moderate	Moderate	Low	Moderate	Low	Moderate
U. Herrlinger et al., 2017 [54]	Low	Low	Low	Low	Low	Low
P. Lesueur et al., 2025 [55]	Low	Moderate	Low	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Prashasti Sharma et al., 2023 [56]	Moderate	Moderate	Low	Moderate	Low	Moderate
Meihua Wang et al., 2010 [57]	Low	Low	Low	Moderate	Low	Low
Assaf Berger et al., 2018 [58]	Low	Moderate	Low	Moderate	Low	Moderate
M. Klein et al., 2020 [59]	Low	Low	Low	Low	Low	Low
N. Laack et al., 2018 [60]	Low	Low	Low	Low	Low	Low
Kristin M. Huntoon et al., 2022 [61]	Low	Low	Low	Moderate	Low	Low
Xuyun Xie et al., 2023 [62]	Moderate	Moderate	Low	Moderate	Low	Moderate
C. Chung et al., 2017 [23]	Low	Low	Low	Moderate	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
M. Chan et al., 2020 [15]	Low	Moderate	Low	Moderate	Low	Moderate
I. Rydén et al., 2025 [63]	Low	Low	Low	Low	Low	Low
K. Tringale et al., 2017 [13]	Low	Moderate	Low	Moderate	Low	Moderate
S. Rapp et al., 2013 [64]	Low	Low	Low	Moderate	Low	Low
P. Pospíšil et al., 2017 [65]	Low	Moderate	Low	Moderate	Low	Moderate
Narendra Kumar et al., 2019 [66]	Moderate	Moderate	Low	High	Moderate	High
Sandra Leskinen et al., 2023 [67]	Low	Low	Low	Low	Low	Low
D. Correa, 2021 [68]	Low	Low	Low	Low	Low	Low
E. Chang, 2017 [69]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Weijie Shang et al., 2022 [70]	Moderate	Moderate	Low	Moderate	Low	Moderate
B. Corn et al., 2008 [71]	Low	Low	Low	Moderate	Low	Low
E. Shaw et al., 2013 [72]	Low	Low	Low	Moderate	Low	Low
G. Masucci et al., 2021 [73]	Low	Moderate	Low	High	Low	Moderate
C. Cramer et al., 2018 [74]	Low	Low	Low	Low	Low	Low
K. Edelstein et al., 2014 [75]	Moderate	Moderate	Low	High	Moderate	High
Buhai Wang et al., 2021 [76]	Moderate	Moderate	Low	Moderate	Low	Moderate
K. Peters et al., 2022 [77]	Low	Moderate	Low	Moderate	Low	Moderate
Shinn-yn Lin et al., 2015 [78]	Low	Moderate	Low	Moderate	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
A. Rydelius et al., 2018 [79]	Moderate	Moderate	Low	Moderate	Low	Moderate
Toshimichi Nakano et al., 2018 [16]	Low	Moderate	Low	Low	Low	Low
M. Naughton et al., 2018 [21]	Low	Low	Low	Low	Low	Low
S. Fox et al., 2006 [80]	Low	Low	Low	Moderate	Low	Low

RESULTS

Characteristics of Included Studies

The 80 sources included in this review encompass a broad range of study designs, patient populations, radiotherapy modalities, and cognitive outcomes. The table below summarizes the key characteristics of each included study.

Study	Population	Radiotherapy modality	Primary cognitive research question
P. Brown et al., 2016 [1]	Brain metastases (1–3) [1]	SRS alone vs. SRS + WBRT [1]	Cognitive deterioration at 3 months post-SRS [1]

Study	Population	Radiotherapy modality	Primary cognitive research question
C. Armstrong et al., 2012 [25]	Low-grade supratentorial tumors (n=41 irradiated) [25]	3D-conformal RT, median 54 Gy [25]	Phase effects of RT on semantic vs. perceptual memory [25]
E. V. van Grinsven et al., 2021 [4]	Brain metastases (751 WBRT, 300 SRS) [4]	WBRT and SRS, various schedules [4]	Impact of WBRT vs. SRS on neurocognitive functioning [4]
J. Palmer et al., 2022 [26]	Resected brain metastases, long-term survivors (n=54) [26]	SRS vs. WBRT postoperatively [26]	Long-term cognitive and QOL outcomes in survivors [26]
S. Gudipati et al., 2022 [11]	Primary brain tumor patients (n=63) [11]	Fractionated RT [11]	Thalamus and thalamic nuclei microstructural injury and cognition [11]
M. Salans et al., 2020 [27]	Primary brain tumors (n=59) [27]	Fractionated brain RT [27]	Independent association of QOL with neurocognitive function [27]
W. Schimmel et al., 2022 [28]	Brain metastases 11–20 (n=41) [28]	Gamma Knife SRS vs. WBRT [28]	Cognitive performance after SRS or WBRT in high-burden BM [28]

Study	Population	Radiotherapy modality	Primary cognitive research question
K. Redmond et al., 2015 [29]	Newly diagnosed GBM (n=30) [29]	IMRT 60 Gy/30 fr with NPC sparing [29]	Cognitive effects of NPC-sparing RT in GBM [29]
F. Yang et al., 2022 [9]	Newly diagnosed GBM (n=133) [9]	60 Gy/30 fr vs. 60 Gy/20 fr with chemoRT [9]	Hippocampal dose as predictor of MMSE decline [9]
J. Yu et al., 2021 [12]	Primary brain tumors, 50% glioma (n=50) [12]	Fractionated partial brain RT [12]	Entorhinal cortical volume and memory after RT [12]
Connor Puett et al., 2025 [14]	Metastatic brain disease (n=78) [14]	Cognitive-sparing SRS with WMT and HC constraints [14]	Preservation of cognition with cognitive-sparing SRS [14]
D. M. J. Pelak et al., 2025 [24]	IDH1/2-mutant G2/G3 glioma (n=30) [24]	Pencil-beam scanning PBT, 54–60 Gy(RBE) [24]	PROs and neurocognitive outcomes after PBT [24]
E. Lehrer et al., 2019 [2]	Brain metastases (n=1,005) [2]	WBRT, SRS, WBRT+memantine, HA-WBRT [2]	Comparative cognitive failure rates across modalities [2]

Study	Population	Radiotherapy modality	Primary cognitive research question
J. Kirkpatrick et al., 2020 [30]	Brain metastases >10 (n=5 lead-in, 64 planned) [30]	WBRT 30 Gy/10 fr ± BMX-001 [30]	Neurocognitive preservation with superoxide dismutase mimetic [30]
C. Hahn et al., 2005 [31]	Primary brain tumors (n=11, 6 completed) [31]	3D-conformal RT (>30–40 Gy) [31]	PET-based dose-dependent metabolic and cognitive changes [31]
T. Lawrie et al., 2019 [32]	Low-grade glioma (total 2,406) [32]	RT vs. no RT; high vs. low dose; various schedules [32]	Long-term neurocognitive effects of RT in glioma [32]
R. Farjam et al., 2015 [10]	Low-grade glioma and benign tumors (n=27; 19 completed) [10]	3D-conformal or IMRT, median 54 Gy [10]	Hippocampal vascular injury as predictor of late cognitive decline [10]
N. Laack et al., 2005 [5]	Supratentorial low-grade glioma (n=20) [5]	Localized RT, 50.4 or 64.8 Gy [5]	Cognitive function after RT over 5 years [5]
J. Jaspers et al., 2025 [6]	IDH-mutant G2/G3 glioma (n=49) [6]	Partial brain RT, 50.4–59.4 Gy [6]	Effect of mean brain dose on neurocognitive outcomes [6]

Study	Population	Radiotherapy modality	Primary cognitive research question
Jianpeng Ma et al., 2024 [33]	Mixed brain tumors (n=144; low vs. high dose) [33]	RT, low dose (≤ 30 Gy) vs. high dose (> 30 Gy) [33]	Effect of RT dose on cognitive impairment and psychological status [33]
H. Aoyama et al., 2007 [34]	Brain metastases 1–4 (n=110) [34]	WBRT+SRS vs. SRS alone [34]	Effect of WBRT omission on MMSE [34]
A. Tallet et al., 2012 [3]	Brain metastases, various [3]	WBRT, various schedules [3]	Incidence, magnitude, and timing of WBRT-induced cognitive decline [3]
S. Rapp et al., 2015 [17]	Post-irradiation brain tumor survivors (n=198) [17]	Partial or whole brain (≥ 6 months prior) [17]	Donepezil for cognitive impairment after RT [17]
T. Armstrong et al., 2013 [35]	Newly diagnosed GBM (n=182 subset) [35]	ChemoRT $\pm$ dose-dense TMZ [35]	Net clinical benefit of RT on neurocognition in GBM [35]
Ansa Maer Cole et al., 2013 [36]	Brain metastases (n=50 TG; 27 CG breast cancer) [36]	Whole or partial brain RT [36]	Self-reported cognitive outcomes before and after RT [36]

Study	Population	Radiotherapy modality	Primary cognitive research question
P. Brown et al., 2021 [22]	Newly diagnosed GBM (n=67 evaluable) [22]	Proton RT vs. IMRT [22]	Time to cognitive failure: proton vs. photon RT in GBM [22]
B. Fisher et al., 2005 [37]	Primary CNS lymphoma (n=40 for MMSE) [37]	WBRT 45 Gy/25 fr vs. HFX 36 Gy/30 fr [37]	Cognitive function and neurotoxicity with reduced-dose WBRT in PCNSL [37]
J. Butler et al., 2007 [38]	Primary or metastatic brain tumors (n=68) [38]	Brain RT (various) [38]	Prophylactic d-MPH on QOL and cognitive function during RT [38]
C. Koutsarnakis et al., 2021 [39]	Grade II glioma, adult [39]	Postoperative RT [39]	Neuropsychological effects of RT in grade II glioma [39]
Nicholas F. Marko & R. Weil, 2010 [40]	Brain metastases [40]	SRS ± WBRT [40]	Neurocognitive effects of SRS with or without WBRT [40]

Study	Population	Radiotherapy modality	Primary cognitive research question
C. Crockett & R. Simões, 2023 [20]	Brain metastases (n=518) [20]	HA-WBRT + memantine vs. WBRT + memantine, 30 Gy/10 fr [20]	Sustained cognitive preservation with HA-WBRT plus memantine (NRG CC001) [20]
M. Naughton et al., 2010 [41]	Post-irradiation brain cancer (n=82) [41]	Whole or partial brain [41]	Relationship between cognitive performance and QOL after RT [41]
M. van der Meulen et al., 2021 [42]	CD20+ B-cell PCNSL (n=125) [42]	WBRT 30 Gy/20 fr (patients ≤60 yr) [42]	Neurocognitive function and radiologic changes in PCNSL after WBRT [42]
M. Tibbs et al., 2019 [18]	Primary brain tumors (n=54) [18]	Brain RT (fractionated) [18]	Depression/anxiety as independent predictors of neurocognitive function [18]
Julia R. Schneider et al., 2017 [43]	Brain metastases 1–3 (n=213) [43]	SRS alone vs. SRS + WBRT [43]	Cognitive effects of WBRT addition to SRS [43]

Study	Population	Radiotherapy modality	Primary cognitive research question
N. Chiannilkulchai et al., 2016 [44]	Primary brain tumors (n=116) [44]	RT (type varies) [44]	Symptom experience and predictors in Thai patients during RT [44]
G. Puglisi et al., 2025 [19]	High-grade wild-type glioma (n=200) [19]	ChemoRT (concurrent) [19]	Hemisphere-specific neurocognitive effects of RT [19]
L. Kępka et al., 2016 [45]	Single resected brain metastasis (n=59) [45]	SRT to tumor bed vs. WBRT 30 Gy/10 fr [45]	Neurological/cognitive failure: SRT-TB vs. WBRT [45]
A. Rydelius et al., 2020 [7]	Malignant glioma (n=32) [7]	Arc-based RT + TMZ [7]	Longitudinal cognitive function after modern RT/chemo [7]
A. Tooze & J. Sheehan, 2018 [46]	Pituitary adenoma (n=51) [46]	GKRS (single fraction) vs. surgery alone [46]	Neurocognitive outcomes after GKRS for pituitary adenoma [46]
B. Page et al., 2015 [47]	Primary brain tumors (n=54) [47]	Brain RT ≥ 45 Gy (whole or partial) [47]	Armodafinil for RT-induced fatigue and cognitive function [47]

Study	Population	Radiotherapy modality	Primary cognitive research question
S. Hardy et al., 2020 [48]	Benign/low-grade tumors (n=19) [48]	Partial brain RT (hypo- or conventionally fractionated) [48]	Amygdala RT dose and emotional/social cognition and depression [48]
R. Prabhu et al., 2014 [49]	WHO grade 2 glioma (n=251) [49]	RT 54 Gy $\pm$ PCV chemotherapy [49]	Effect of adding chemotherapy to RT on MMSE in low-grade glioma [49]
J. Jaspers et al., 2024 [8]	IDH-mutant G2/G3 glioma (n=49) [8]	Photon RT (50.4 or 59.4 Gy), mean brain dose 17.8 Gy [8]	Mean brain dose as predictor of neurocognitive decline [8]
S. Hardy et al., 2023 [50]	Benign and low-grade brain tumors (n=75 planned) [50]	Partial brain RT (hypo- or conventionally fractionated) [50]	RT effects on brain structural/functional integrity and cognition [50]
Tarek Bou Dargham et al., 2025 [51]	Brain metastases (n=6,617) [51]	WBRT and radiosurgery, various [51]	Neurocognitive outcomes across modalities in brain metastases [51]
M. Salans et al., 2021 [52]	Primary brain tumors (n=59) [52]	Brain RT (fractionated) [52]	Independent association of QOL and neurocognitive function [52]

Study	Population	Radiotherapy modality	Primary cognitive research question
Prerana Baruah et al., 2025 [53]	Primary CNS tumors: astrocytoma, GBM, oligodendroglioma (n=25) [53]	IMRT/VMAT, 54–60 Gy [53]	Domain-specific cognitive changes after focal RT [53]
U. Herrlinger et al., 2017 [54]	PCNSL (n=318 per-protocol) [54]	Early WBRT 45 Gy/30 fr vs. no early WBRT [54]	QOL and cognitive impact of early WBRT in PCNSL [54]
P. Lesueur et al., 2025 [55]	Skull base grade I–II meningioma (n=36/cohort) [55]	SRT, IMRT, or proton therapy [55]	Long-term cognitive deterioration after RT for meningioma (up to 10 years) [55]
Prashasti Sharma et al., 2023 [56]	High-grade glioma (n=53) [56]	VMAT 60 Gy/30 fr + TMZ [56]	Risk factors for neurocognitive impairment after chemoRT in HGG [56]
Meihua Wang et al., 2010 [57]	Anaplastic oligodendroglioma (n=289) [57]	RT 59.4 Gy ± PCV chemo [57]	Longitudinal cognition and QOL after RT ± PCV [57]
Assaf Berger et al., 2018 [58]	Brain metastases (n=12 evaluable) [58]	Post-resection SRS [58]	Neurocognitive effects of post-resection SRS [58]

Study	Population	Radiotherapy modality	Primary cognitive research question
M. Klein et al., 2020 [59]	Low-grade glioma G2 (n=98) [59]	RT 50.4 Gy vs. TMZ alone [59]	Memory function: RT vs. TMZ in high-risk LGG [59]
N. Laack et al., 2018 [60]	Brain metastases (n=246 evaluable) [60]	WBRT + placebo vs. memantine [60]	Association of HRQOL with cognitive function during WBRT [60]
Kristin M. Huntoon et al., 2022 [61]	Brain metastases (n=73) [61]	SRS vs. WBRT (postoperative) [61]	Biomarkers (ApoJ, ApoE, ApoA, A β) and cognitive decline after RT [61]
Xuyun Xie et al., 2023 [62]	Brain metastases from lung cancer (n=19) [62]	WBRT [62]	DKI parameters as predictors of cognitive decline after WBRT [62]
C. Chung et al., 2017 [23]	Newly diagnosed GBM (n=75 evaluable) [23]	IMPT vs. IMRT [23]	Time to cognitive failure: proton vs. photon RT in GBM [23]
M. Chan et al., 2020 [15]	Brain metastases (n=46 survivors $\geq$ 3 months) [15]	SRS + WBRT 20 Gy/5 fr [15]	Predictors of cognitive decline after WBRT [15]

Study	Population	Radiotherapy modality	Primary cognitive research question
I. Rydén et al., 2025 [63]	IDH-mutant glioma (n=127) [63]	Multimodal treatment including RT [63]	Cognitive changes 1 year after guideline-based treatment [63]
K. Tringale et al., 2017 [13]	Primary brain tumors, glioma (n=25) [13]	Fractionated partial brain RT (median 54 Gy) [13]	Neuroimaging correlates of verbal/nonverbal memory decline [13]
S. Rapp et al., 2013 [64]	Post-irradiation brain tumor survivors (n=198) [64]	Whole or partial brain (>30 Gy) [64]	Donepezil for cognitive function in RT survivors [64]
P. Pospíšil et al., 2017 [65]	Brain metastases (n=18 completed) [65]	WBRT 30 Gy/10 fr [65]	MR spectroscopy hippocampal NAA as biomarker of cognitive decline [65]
Narendra Kumar et al., 2019 [66]	GBM (n=50) [66]	RTOG vs. MDACC conformal RT protocols [66]	Volume of irradiation, QOL, and survival in GBM [66]
Sandra Leskinen et al., 2023 [67]	Brain metastases predominant (n=1,749) [67]	HA-WBRT and HA-PCI [67]	Hippocampal avoidance: relapse rates and neurocognitive effects [67]

Study	Population	Radiotherapy modality	Primary cognitive research question
D. Correa, 2021 [68]	PCNSL, adult [68]	WBRT (various doses); chemotherapy comparisons [68]	Treatment-related neurotoxicity in PCNSL [68]
E. Chang, 2017 [69]	Brain metastases 1–3 [69]	SRS alone vs. SRS + WBRT [69]	Cognitive preservation in brain metastases treated with SRS [69]
Weijie Shang et al., 2022 [70]	Brain metastases (n=40) [70]	HS-WBRT vs. WBRT, 30 Gy/10 fr [70]	Hippocampal sparing effect on cognitive function and hippocampal volume [70]
B. Corn et al., 2008 [71]	Brain metastases (n=156) [71]	WBRT 37.5 Gy/15 fr ± thalidomide [71]	QOL and neurocognitive outcomes in multiple brain metastases [71]
E. Shaw et al., 2013 [72]	Primary brain tumors (n=54) [72]	Brain RT >45 Gy [72]	Armodafinil for fatigue during brain RT [72]
G. Masucci et al., 2021 [73]	Brain metastases from NSCLC and RCC (n=16 at 3 mo; 9 at 6 mo) [73]	SRS 15–21 Gy + nivolumab [73]	Neurocognitive function after SRS + nivolumab [73]

Study	Population	Radiotherapy modality	Primary cognitive research question
C. Cramer et al., 2018 [74]	Post-RT brain tumor survivors (n=197) [74]	Whole or partial brain (>30 Gy, ≥6 months prior) [74]	Mild cognitive impairment classification in RT survivors [74]
K. Edelstein et al., 2014 [75]	Primary brain tumors (n=21) [75]	Partial or whole brain RT [75]	Longitudinal cognitive changes years after RT [75]
Buhai Wang et al., 2021 [76]	Brain metastases from NSCLC (n=47) [76]	HA-WBRT (n=27) vs. WBRT (n=20), 30 Gy/10 fr [76]	Long-term neurocognitive preservation with HA-WBRT [76]
K. Peters et al., 2022 [77]	WHO grade 4 GBM (n=15) [77]	RT 59.4–60 Gy + TMZ + BMX-001 [77]	Neurocognitive outcomes with BMX-001 during RT/TMZ [77]
Shinn-yn Lin et al., 2015 [78]	Brain metastases (n=25) [78]	HA-WBRT 30 Gy/12 fr (VMAT) [78]	Neurocognitive preservation with hippocampal-sparing WBRT [78]
A. Rydelius et al., 2018 [79]	GBM (n=29 implied) [79]	RT + concomitant TMZ [79]	DTI microstructural changes after RT in GBM [79]

Study	Population	Radiotherapy modality	Primary cognitive research question
Toshimichi Nakano et al., 2018 [16]	Brain metastases (n=41) [16]	WBRT (25–35 Gy in 10–14 fr) [16]	Risk factors for early cognitive deterioration after WBRT [16]
M. Naughton et al., 2018 [21]	Post-RT brain tumor survivors (n=198) [21]	Whole or partial brain (≥ 30 Gy, ≥ 6 months prior) [21]	QOL after donepezil or placebo in irradiated survivors [21]
S. Fox et al., 2006 [80]	Brain metastases (n=176) [80]	WBRT 37.5 Gy/15 fr $\pm$ thalidomide [80]	Neurocognitive progression and QOL relationship in WBRT patients [80]

Baseline cognitive impairment was common across all populations. Among brain metastasis patients undergoing WBRT, 91% displayed some degree of cognitive impairment before treatment [4]. Among post-irradiation brain tumor survivors enrolled in the donepezil trial, 66% met NIA-AA criteria for mild cognitive impairment at baseline [74]. In the HOVON 105 PCNSL cohort, 90% had impairments in at least one neurocognitive domain before any treatment [42]. These findings underscore the importance of separating disease-related from treatment-related cognitive effects, a methodological challenge explicitly noted across numerous studies [10–12, 25].

Effects of Radiotherapy on Cognitive Function

Summary of Cognitive Outcomes Across Modalities and Populations

The table below presents quantitative cognitive outcome data extracted from included studies, organized by radiotherapy modality.

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
P. Brown et al., 2016 [1]	SRS alone vs. SRS+WBRT	Immediate/delayed memory, verbal fluency	Cognitive deterioration: 63.5% (SRS) vs. 91.7% (SRS+WBRT); difference -28.2% (90% CI -41.9% to -14.4%), $p < 0.001$ [1]	3 months; n=213
J. Palmer et al., 2022 [26]	SRS vs. WBRT (postoperative)	Multiple domains	Cognitive deterioration 37%–60% (SRS) vs. 75%–91% (WBRT); 2 SD decline in ≥ 1 test at 3 months: 22% vs. 70% [26]	3, 6, 9 months; n=54 long-term survivors
E. V. van Grinsven et al., 2021 [4]	WBRT vs. SRS	Learning and memory, EF, verbal fluency	WBRT: 19–37% of patients decline in learning/memory; SRS: majority return to baseline by ~5 months [4]	Up to 15 months
W. Schimmel et al., 2022 [28]	GKRS vs. WBRT (11–20 BM)	Immediate recall, delayed recall, processing speed	HVLT-R TR failure rates: GKRS 31% vs. WBRT 29% at 3 months; 0% vs. 33% at 6 months; large effect sizes [28]	3 and 6 months; n=41

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
E. Lehrer et al., 2019 [2]	WBRT, SRS, WBRT+M, HA-WBRT	General cognition	Cognitive failure summary effects: WBRT 53.2%, WBRT+M 43.7%, HA-WBRT 33.3%, SRS 20.9% [2]	3–4 months; n=1,005
H. Aoyama et al., 2007 [34]	WBRT+SRS vs. SRS alone	MMSE	Mean time to 3-point MMSE drop: 16.5 months (WBRT+SRS) vs. 7.6 months (SRS alone), p=0.05 [34]	12, 24, 36 months; n=110
L. Kępka et al., 2016 [45]	SRT-TB vs. WBRT (resected single BM)	Neurological/cognitive failure	2-year cumulative incidence of neurological/cognitive failure: 66% (SRT-TB) vs. 31% (WBRT), p=0.015 [45]	6 months–2 years; n=59
Weijie Shang et al., 2022 [70]	HS-WBRT vs. WBRT	MoCA (multiple domains)	Significantly higher MoCA scores at 3, 6, and 12 months in HS-WBRT group (p<0.05) [70]	3, 6, 12 months; n=40

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
Buhai Wang et al., 2021 [76]	HA-WBRT vs. WBRT	MMSE, MoCA	Significantly higher cognitive scores at 12 and 24 months in HA-WBRT group ($p<0.001$) [76]	Up to 24 months; $n=47$
C. Crockett & R. Simões, 2023 [20]	HA-WBRT+memantine vs. WBRT+memantine	HVLT-R, COWA, TMT	Cognitive failure prevention: adjusted HR=0.74, $p=0.016$; younger patients (≤ 61 yr) HR=0.61 [20]	Median 12.1 months; $n=518$
Sandra Leskinen et al., 2023 [67]	HA-WBRT / HA-PCI	Overall cognition, memory/verbal learning	Significant differences in overall cognitive function and memory/verbal learning 3–24 months post-RT [67]	3–24 months; $n=1,749$
Shinn-yn Lin et al., 2015 [78]	HA-WBRT (VMAT)	Delayed verbal memory	Significant decline in delayed recall: $F=5.727$, $p=0.048$; other domains largely preserved [78]	4 and 12 months; $n=25$

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
P. Pospíšil et al., 2017 [65]	WBRT 30 Gy/10 fr	Memory (AVLT, BVMT-R)	Hippocampal h-tNAA decreased 12.9% (right) and 12.0% (left); significant decline in all memory subtests except AVLT Recognition; QOL declined -14.1 points (p=0.018) [65]	4 months; n=18
A. Tallet et al., 2012 [3]	WBRT	Memory, EF	Cognitive decline predominant at 4 months; only 8% grade ≥ 2 (SOMA-LENT); peak decline at 4 months [3]	Up to 36 months
Toshimichi Nakano et al., 2018 [16]	WBRT	HVLT-R total recall, delayed recognition	Significant declines in TR (p=0.01) and DRecog (p=0.01) in all patients; worse in ≥ 65 yr and intracranial PD groups [16]	4 and 8 months; n=41
B. Corn et al., 2008 [71]	WBRT $\pm$ thalidomide	MMSE	MMSE failures increased 60% by 6 months on both arms; QOL remained stable [71]	Up to 6 months; n=156

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
S. Fox et al., 2006 [80]	WBRT ± thalidomide	MMSE	MMSE failures increased 60% by 6 months; 43% below cutoff at baseline [80]	Up to 6 months; n=176
M. Chan et al., 2020 [15]	SRS + WBRT	MoCA	Every patient >70 years experienced cognitive decline; age OR 1.12 (p<0.01); Fazekas ≥3 OR 6.4 (p<0.01) [15]	Up to 1 year; n=46
Xuyun Xie et al., 2023 [62]	WBRT	MMSE	RCI-PE declined at 2–6 months post-WBRT (mean −0.842, 95% CI −0.376 to −1.310, p=0.002) [62]	2–6 months; n=19
Jianpeng Ma et al., 2024 [33]	RT low dose vs. high dose	MMSE	Lower MMSE in high-dose group at months 1 and 3; worsened role functioning and depression at month 3 [33]	Up to 9 months; n=144
P. Brown et al., 2021 [22]	Proton RT vs. IMRT (GBM)	Multiple domains	No significant difference in time to cognitive failure: HR 0.88 (95% CI 0.45–1.75), p=0.74 [22]	Median 48.7 months; n=67

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
C. Chung et al., 2017 [23]	IMPT vs. IMRT (GBM)	HVLT-R, TMT, COWA	Cumulative cognitive deterioration at 4 months: 59.3% (IMPT) vs. 37.2% (IMRT); time to cognitive failure shorter with IMPT ($p<0.05$) [23]	Median 14.5 months; n=75
D. M. J. Pelak et al., 2025 [24]	PBT for IDH-mutant glioma	HVLT-R, TMT, COWA	No significant decline in most scales; COWA verbal fluency improved ($\beta=0.07$, $p<0.001$) [24]	Median 62.5 months; n=30
J. Jaspers et al., 2025 [6]	Photon RT for IDH-mutant glioma	HVLT, TMT, Letter Fluency	No decline in test performance over time ($p\geq 0.526$); negative effect of mean brain dose on TMT-A ($\beta=-0.11$, $p=0.008$) and TMT-B ($\beta=-0.13$, $p=0.004$) [6]	Median 5.8 years; n=49
J. Jaspers et al., 2024 [8]	Photon RT for IDH-mutant glioma	HVLT, TMT, LF	No decline over time; inverse relationship between mean brain dose and 4 of 5 tests ($p<0.02$) [8]	Median 5.8 years; n=49

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
N. Laack et al., 2005 [5]	Localized RT 50.4 or 64.8 Gy (LGG)	Broad neuropsychological battery	Cognitive function stable; slight improvements consistent with practice effects [5]	Up to 5 years; n=20
A. Rydelius et al., 2020 [7]	Arc-based RT + TMZ (malignant glioma)	CNS-VS (9 domains)	Significant changes only in visual memory at 3.5 and 12 months; other domains stable [7]	Up to 12 months; n=32
Meihua Wang et al., 2010 [57]	RT ± PCV (anaplastic oligodendroglioma)	MMSE	MMSE stable in survivors (p=0.0413 aggregate decline over time); no difference between arms (p=0.4752) [57]	Up to 5 years; n=289
R. Prabhu et al., 2014 [49]	RT ± PCV (WHO grade 2 glioma)	MMSE	Few significant declines; both arms showed mean MMSE score increase over time; no between-arm difference [49]	Up to 5 years; n=251

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
M. Klein et al., 2020 [59]	RT vs. TMZ (high-risk LGG)	VVLT (memory)	No significant difference between RT and TMZ in memory functioning; delayed recovery in RT group [59]	Up to 12 months; n=98
G. Puglisi et al., 2025 [19]	ChemoRT (high-grade glioma)	Language, attention, EF, praxis	Greatest decline 1 month post-treatment across all domains; left hemisphere: selective language impairment; right hemisphere: attention/EF impairment; gradual recovery from 3 months [19]	Up to 12 months; n=200
I. Rydén et al., 2025 [63]	Multimodal treatment including RT (IDH-mutant glioma)	Broad NP battery	Declines: EF 24%, learning/memory 23%, language 21%; inhibition/flexibility 32%, naming speed 29%, verbal memory 28% [63]	1 year; n=127

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
Prashasti Sharma et al., 2023 [56]	VMAT 60 Gy/30 fr + TMZ (HGG)	MMSE	56.6% developed cognitive impairment; mean MMSE declined from 28.92 to 22.96; 66.7% with progression had CI vs. 28.6% without [56]	Median 15 months; n=53
M. van der Meulen et al., 2021 [42]	WBRT 30 Gy in PCNSL (≤ 60 yr)	Multiple NP tests	Statistically significant improvements in all domains; clinically relevant improvement only in motor speed; stable after WBRT in follow-up (no further decline) [42]	Up to 2 years; n=43 irradiated
U. Herrlinger et al., 2017 [54]	Early WBRT 45 Gy vs. no early WBRT (PCNSL)	MMSE, EORTC-QLQ	Reduced cognitive function and global health at year 2 in early WBRT arm (p=0.004 and p=0.022); lower MMSE (p=0.002) [54]	Up to 4 years; n=318

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
D. Correa, 2021 [68]	WBRT vs. chemo alone (PCNSL)	Multiple NP tests	High prevalence of cognitive dysfunction post-WBRT; stable or improved with HD-MTX alone; reduced-dose WBRT associated with less neurotoxicity [68]	Months to years
K. Redmond et al., 2015 [29]	IMRT 60 Gy/30 fr with NPC sparing (GBM)	Processing speed (Coding)	Higher mean RT dose to bilateral SVZ associated with greater deterioration in processing speed at 6/12 months (p=0.03) [29]	Up to 24 months; n=30
F. Yang et al., 2022 [9]	Short-course vs. conventional chemoRT (GBM)	MMSE	Mean left hippocampus dose significantly associated with MMSE decline (p=0.005) [9]	Post-RT; n=133
C. Hahn et al., 2005 [31]	3D-conformal RT (CNS tumors)	Wisconsin Card Sorting Test	Average T-score decrease of 11 on WCST (p=0.037); reduced FDG uptake 2–6% in regions receiving >40 Gy [31]	3 weeks and 6 months; n=6

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
K. Tringale et al., 2017 [13]	Fractionated partial brain RT	BVMT (nonverbal memory), HVLТ (verbal memory)	Significant decline in nonverbal learning (BVMT total recall, $p=0.009$); verbal memory stable; glioma patients and chemotherapy recipients most affected [13]	6 months; $n=25$
S. Gudipati et al., 2022 [11]	Fractionated RT (primary brain tumors)	EF (DKEFS-LF), visuospatial memory (BVMT), attention (WAIS-IV DSF)	Thalamic microstructural injury dose-dependent and progressive; decreased thalamic FA predicted worse DKEFS letter fluency ($p=0.013-0.048$) [11]	Up to 12 months; $n=63$
Prerana Baruah et al., 2025 [53]	IMRT/VMAT (focal RT, CNS tumors)	ACE-III (attention, language, fluency most affected)	Mean ACE-III declined from 89.48 to 87.91 ($p=0.007$); corpus callosum dose 35.91 Gy (decline group) vs. 30.70 Gy (no decline) [53]	6 months; $n=25$

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
M. Tibbs et al., 2019 [18]	Brain RT (primary tumors)	Attention/processing speed, EF, memory	Anxiety independently predicted decline in DKEFS-TMT (all 3 subtests, $p<0.001-0.011$); depression predicted DKEFS TMT Letter Sequencing decline ($p=0.013$) [18]	Up to 12 months; n=54
C. Armstrong et al., 2012 [25]	3D-conformal RT (low-grade supratentorial)	Semantic memory retrieval	Cohen's $d=0.50$ for RAVLT; significant effects on delayed recall ($p<0.009$) and interval to recognize ($p<0.002$) in RT group only [25]	Up to 1 year; n=41 irradiated
J. Yu et al., 2021 [12]	Fractionated partial brain RT	Verbal and visuospatial memory	HVLT-Total RCI=-0.74 ($p=0.032$); HVLT-Delayed RCI=-1.39 ($p<0.001$); BVMT-Total RCI=-0.64 ($p=0.034$) [12]	Up to 12 months; n=50

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
Connor Puett et al., 2025 [14]	Cognitive-sparing SRS (metastatic)	Memory, language, EF, attention, fine motor	No significant cognitive decline overall ($p>0.1$); patients not meeting WMT dose constraints showed greater memory decline ($p=0.02$) [14]	3 months; n=78
K. Peters et al., 2022 [77]	RT + TMZ + BMX-001 (GBM)	Multiple domains (CNS Vital Signs)	Most testing demonstrated improved performance at 2 and 6 months post-RT [77]	Up to 6 months; n=15
Assaf Berger et al., 2018 [58]	Post-resection SRS	Global cognitive, verbal memory, EF	No significant overall change; patients <60 yr: global score increased 88→95 ($p=0.042$); verbal memory and EF scores increased ($p=0.043$) [58]	3 months; n=12
A. Tooze & J. Sheehan, 2018 [46]	GKRS for pituitary adenoma	Anterograde memory (visual)	Significant memory impairment in entire sample; no significant difference in memory scores between GKRS and non-GKRS groups [46]	Cross-sectional; n=51

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
G. Masucci et al., 2021 [73]	SRS + nivolumab (NSCLC/RCC BM)	HVLT-R, TMT, COWA	50% showed ≥ 1 SD deterioration at 3 months; significant improvement on TMT-A ($p=0.04$) and TMT-B ($p=0.03$) at 6 months [73]	Up to 6 months; n=16/9
S. Rapp et al., 2015 [17]	Post-RT (partial/whole brain) + donepezil vs. placebo	Memory, motor speed, attention	No significant composite score difference ($p=0.48$); improvements in memory recognition ($p=0.027$), discrimination ($p=0.007$), motor speed ($p=0.016$) with donepezil [17]	24 weeks; n=198
M. Naughton et al., 2018 [21]	Post-RT + donepezil vs. placebo	FACT-Br, FACIT-fatigue	Positive donepezil HRQL impact greater in more symptomatic patients; worse functional well-being and fatigue in less symptomatic patients receiving donepezil [21]	12 and 24 weeks; n=198

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
N. Laack et al., 2018 [60]	WBRT + memantine vs. placebo	Multiple NP domains	All objective cognitive domains declined over time; no by-arm HRQOL differences despite differences in objective cognition [60]	24 weeks; n=246
B. Fisher et al., 2005 [37]	WBRT 45 Gy/25 fr vs. HFX 36 Gy/30 fr (PCNSL)	MMSE	MMSE improved at 8 months in both groups; no significant difference between RT and HFX (p=0.81); HFX delayed but did not eliminate leukoencephalopathy [37]	8 months; n=40
S. Hardy et al., 2020 [48]	Partial brain RT (benign/low-grade)	Emotion recognition, depression	Higher RT dose to amygdala correlated with increased depressive symptoms (left: rho=0.50, p=0.035; right: rho=0.48, p=0.044) [48]	3 months; n=19

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
Ansa Maer Cole et al., 2013 [36]	Whole or partial brain RT (BM)	Attention (FEDA), memory (FEAG)	Significant decline in fatigue/retardation ($p=0.002$) and motivation ($p=0.032$) in treatment group; less decline in motivation with hypofractionated SRT vs. WBRT ($p=0.025$) [36]	Up to 6 months; $n=50$
R. Farjam et al., 2015 [10]	3D-conformal or IMRT, median 54 Gy	Verbal memory (HVLt-R)	Z-score decline of -0.97 in delayed recall; left hippocampal vascular response correlated with memory at 6 months ($r=-0.95$, $p=0.0006$) and 18 months ($r=-0.88$, $p=0.02$) in females [10]	Up to 18 months; $n=19$
C. Cramer et al., 2018 [74]	Post-RT (whole or partial)	Multiple NP domains	66% met NIA-AA MCI criteria: 13% aMCI-sd, 58% aMCI-md, 19% naMCI-sd, 10% naMCI-md [74]	≥ 6 months post-RT; $n=197$

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
K. Edelstein et al., 2014 [75]	Partial or whole brain RT	Processing speed, attention, memory, EF	Progressive cognitive changes over years post-RT [75]	Up to 6.77 years; n=21
M. Naughton et al., 2010 [41]	Post-irradiation brain tumors	COWA, HVLTR, TMT, Digit Span, Pegboard	Cognitive performance related to QOL; specific domain data not reported in abstract [41]	Baseline; n=82
T. Armstrong et al., 2013 [35]	ChemoRT (standard vs. dose-dense TMZ, GBM)	HVLT-R, TMT, COWA	No NCF difference between arms; greater QOL/symptom burden in dose-dense arm [35]	Baseline to cycle 4; n=182
N. Chiannilkulchai et al., 2016 [44]	Brain RT (various, Thai patients)	MMSE (difficulty remembering)	Difficulty remembering predicted by RT type, tumor laterality, and tumor location [44]	During RT; n=116
B. Page et al., 2015 [47]	Brain RT + armodafinil vs. placebo	Verbal fluency, HVLT-R, TMT, DST	No significant group differences overall; patients with greater baseline fatigue benefited from armodafinil [47]	End of RT + 4 weeks; n=54

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
J. Butler et al., 2007 [38]	Brain RT + d-MPH vs. placebo	MMSE, FACIT-F	No improvement in QOL or secondary cognitive outcomes with prophylactic d-MPH [38]	8 and 12 weeks; n=68
T. Lawrie et al., 2019 [32]	RT vs. no RT (LGG); high vs. low dose; various	Broad NP batteries, MMSE	RT risk RR 1.95 (95% CI 1.02–3.71) for cognitive impairment at 12 years; no clear difference at 5–6 years; no effect of adding PCV on MMSE [32]	2–12 years; n=2,406 total
Narendra Kumar et al., 2019 [66]	RTOG vs. MDACC RT protocols (GBM)	EORTC QLQ cognitive domain	No significant difference between protocols in cognitive QOL [66]	Not specified; n=50
M. Salans et al., 2020 [27]	Fractionated brain RT (primary tumors)	Memory, EF, attention	Physical/functional hrQOL independently associated with better memory and EF (p=0.004–0.047) [27]	Up to 12 months; n=59

Study	Modality	Key cognitive domain(s)	Primary quantitative finding	Comparison / follow-up
M. Salans et al., 2021 [52]	Fractionated brain RT (primary tumors)	Memory, EF, processing speed	Higher physical hrQOL: better verbal memory (p=0.047); higher functional hrQOL: better EF (p=0.009) and verbal memory (p=0.006) [52]	Up to 12 months; n=59
C. Crockett & R. Simões, 2023 (NRG CC001) [20]	HA-WBRT+memantine vs. WBRT+memantine	HVLT-R, COWA, TMT	Adjusted HR=0.74 (p=0.016) for cognitive failure prevention; less symptom interference at 6 and 12 months [20]	Median 12.1 months; n=518
Kristin M. Huntoon et al., 2022 [61]	SRS vs. WBRT (postoperative BM)	General (biomarker study)	Low ApoJ, ApoE, ApoA (p<0.01) and high Aβ1-42 (p=0.048) at baseline associated with cognitive decline at 3 months post-SRS [61]	3 months; n=73

The breadth of quantitative data reveals a consistent hierarchy of cognitive toxicity across modalities, with WBRT reliably producing the most severe and prevalent cognitive decline, particularly in memory and processing speed. SRS-based approaches produce substantially less cognitive morbidity, and techniques that preserve neural structures (hippocampal avoidance, white

matter tract sparing) attenuate cognitive consequences further. The following subsections examine these effects in detail by population and modality.

Cognitive Effects of Whole-Brain Radiotherapy

WBRT produces the most consistently documented and quantitatively severe cognitive decline of any radiotherapy modality. In the large randomized trial by P. Brown et al. (2016), 91.7% of patients receiving SRS combined with WBRT experienced cognitive deterioration at 3 months, compared with 63.5% in the SRS-alone group, a statistically significant difference of -28.2% (90% CI -41.9% to -14.4% , $p < 0.001$) [1]. Similarly, J. Palmer et al. (2022) found that 70% of long-term WBRT recipients declined by ≥ 2 standard deviations on at least one cognitive test at 3 months, versus only 22% in the SRS arm [26]. These declines were clinically meaningful: a ≥ 2 SD decline in ≥ 2 cognitive tests was associated with worse 12-month QOL across emotional, functional, and global domains [26].

E. Lehrer et al. (2019) quantified cognitive failure rates across modalities in 1,005 patients: WBRT yielded a summary cognitive failure rate of 53.2% (95% CI 48.5%–57.8%), compared with 20.9% for SRS (95% CI 15.7%–26.7%), 43.7% for WBRT plus memantine, and 33.3% for HA-WBRT—all assessed at 3–4 months [2]. MMSE-based evidence from Toshimichi Nakano et al. (2018) identified significant declines in total recall ($p = 0.01$) and delayed recognition ($p = 0.01$) at 4 months post-WBRT across all 41 patients, with greater deterioration in patients aged ≥ 65 years, those with worse prognostic scores, and those with intracranial progressive disease [16].

The temporal pattern of WBRT-related cognitive decline is well-characterized. A. Tallet et al. (2012) synthesized the literature showing peak cognitive decline at 4 months, with evidence of partial recovery at later time points in patients with controlled brain disease, and progression of impairment in those with uncontrolled disease [3, 3]. The systematic review by E. V. van Grinsven et al. (2021) corroborated this: WBRT patients showed stabilization or return to baseline at 9–15 months in those who survived that long, while SRS-related cognitive effects were largely transient, with most patients returning to baseline within 5 months [4]. M. S. Fox et al. (2006) documented a 60% increase in MMSE failures at 6 months post-WBRT, independent of thalidomide addition [80].

In the context of PCNSL, WBRT carries particularly severe long-term neurological consequences. U. Herrlinger et al. (2017) found that early WBRT (45 Gy) in PCNSL led to significantly worse cognitive function and global health status at 2 years compared with chemotherapy alone ($p=0.004$ and $p=0.022$ respectively), with lower MMSE scores ($p=0.002$) and greater fatigue [54]. Similarly, D. Correa (2021) reviewed evidence showing that HD-MTX-based chemotherapy alone was associated with stable or improved cognitive functioning in PCNSL, while consolidation WBRT consistently produced cognitive decline and white matter abnormalities in most patients [68]. B. Fisher et al. (2005) found that reducing the WBRT dose from 45 Gy/25 fr to 36 Gy/30 fr (hyperfractionated) delayed but did not eliminate leukoencephalopathy in PCNSL patients [37].

The risk of WBRT-induced cognitive decline is further modulated by patient characteristics. M. Chan et al. (2020) identified age (OR 1.12 per year, $p<0.01$), baseline white matter hyperintensity (WMH) volume (OR 1.20, $p=0.02$), and Fazekas score ≥ 3 (OR 6.4, $p<0.01$) as significant predictors of cognitive decline after WBRT; all three patients with pre-treatment leukoencephalopathy (Fazekas=6/6) suffered severe outcomes, including institutionalization [15]. Toshimichi Nakano et al. (2018) similarly found that age ≥ 65 years, poor prognostic score, and intracranial progressive disease all predicted worse cognitive trajectories after WBRT [16].

Cognitive Effects of Stereotactic Radiosurgery

In contrast to WBRT, SRS consistently produces less cognitive morbidity. In the randomized trial of H. Aoyama et al. (2007), the average time to a 3-point MMSE deterioration was 7.6 months in the SRS-alone group compared with 16.5 months in the WBRT+SRS group ($p=0.05$), reflecting that while WBRT initially delays MMSE decline by protecting tumor control, its long-term cognitive toxicity eventually predominates [34]. This finding is notable because it demonstrates that improved intracranial control via WBRT did not translate into improved long-term cognitive preservation.

Assaf Berger et al. (2018) found that post-resection SRS had a safe neurocognitive profile, with no significant overall cognitive changes at 3 months; patients younger than 60 years actually showed cognitive improvement (global score from 88 to 95, $p=0.042$) and improvements in verbal

memory and executive function [58]. The COG-SRS trial (Connor Puett et al., 2025) demonstrated that a connectivity-informed, cognitive-sparing SRS approach using white matter tract and hippocampal dose constraints ($D_{max} \leq 12$ Gy for WMT, ≤ 8.4 Gy for hippocampus) achieved no significant cognitive decline from baseline to 3 months post-SRS, with local control of 98% at 12 months [14]. Patients whose tumors could not be planned within these constraints showed significantly greater memory decline ($p=0.02$) [14].

In the interim analysis of the CAR-Study B (W. Schimmel et al., 2022), even among patients with 11–20 brain metastases—a population historically considered unsuitable for SRS—HVL-T-R total recall failure rates at 6 months were 0% for GKRS versus 33% for WBRT, with large effect sizes favoring SRS [28]. No patients in the GKRS group experienced declines across all tests at the individual level, while 4 of 8 WBRT patients did [28].

G. Masucci et al. (2021) evaluated SRS combined with nivolumab for NSCLC/RCC brain metastases. At 3 months, 50% of patients showed ≥ 1 SD deterioration on at least one test from baseline, but at 6 months, significant improvements on TMT-A ($p=0.04$) and TMT-B ($p=0.03$) were observed among patients who survived to that timepoint—suggesting that the early decline was transient and potentially tumor-related rather than treatment-related [73].

Hippocampal Avoidance and Neuroprotective Radiotherapy Modifications

A substantial body of evidence supports hippocampal avoidance as an effective strategy for reducing RT-induced cognitive decline in the context of WBRT. The NRG CC001 trial (reported in C. Crockett & R. Simões, 2023) randomized 518 patients to HA-WBRT plus memantine versus WBRT plus memantine, demonstrating that hippocampal avoidance significantly reduced cognitive failure (adjusted HR=0.74, $p=0.016$), with younger patients (≤ 61 years) benefiting most (HR=0.61) [20]. Patients in the HA-WBRT arm reported less symptom interference in daily life at 6 months and reduced symptom burden at 12 months, with no difference in overall survival or intracranial progression-free survival [20].

Buhai Wang et al. (2021) showed, in a retrospective cohort, that HA-WBRT resulted in significantly higher MMSE and MoCA scores at 12 and 24 months compared with standard WBRT ($p<0.001$), with smaller hippocampal volume loss in the HA-WBRT group [76]. Weijie Shang et al.

(2022) similarly found significantly higher MoCA scores at 3, 6, and 12 months in the hippocampal-sparing WBRT group ($p < 0.05$), with better ECOG scores and QLQ-C30 scores [70]. Shinn-yn Lin et al. (2015) reported that HA-WBRT largely preserved cognitive function, with the only significant decline observed in delayed verbal recall ($p = 0.048$) [78]. The systematic meta-analysis by Sandra Leskinen et al. (2023) covering 1,749 patients confirmed that HA-WBRT/HA-PCI produced significant improvements in overall cognitive function and memory/verbal learning at 3–24 months post-RT, with hippocampal relapse rates remaining low (pooled effect size = 0.04, 95% CI 0.03–0.05) and no significant difference in relapse risk between HA-WBRT and conventional WBRT [67].

Cognitive Effects in Primary Brain Tumors: Gliomas and Related Tumors

For patients with primary brain tumors, particularly glioma, the RT-cognition relationship is more complex because tumors themselves cause cognitive impairment [4], making it difficult to disentangle disease from treatment effects [25]. Several prospective studies in low-grade and IDH-mutant glioma have found surprisingly stable cognitive trajectories after RT.

N. Laack et al. (2005) followed 20 patients with supratentorial low-grade glioma receiving 50.4 or 64.8 Gy localized RT for up to 5 years, finding stable cognitive function with slight improvements attributable to practice effects [5]. A. Rydelius et al. (2020) found that arc-based RT with concurrent TMZ produced significant changes only in visual memory at 3.5 and 12 months; eight other cognitive domains remained stable [7]. J. Jaspers et al. (2025) followed 49 IDH-mutant G2/G3 glioma patients for a median of 5.8 years and found no effect of time on test performance ($p \geq 0.526$), though mean brain dose inversely predicted Trail Making Test scores (TMT-A $\beta = -0.11$, $p = 0.008$; TMT-B $\beta = -0.13$, $p = 0.004$) [6]. The companion analysis (J. Jaspers et al., 2024) in the same cohort confirmed this dose-dependent effect, with mean brain dose inversely related to 4 of 5 cognitive test scores ($p < 0.02$) [8].

M. Klein et al. (2020) showed that in high-risk low-grade glioma, RT and temozolomide chemotherapy did not differ significantly in memory outcomes, with both showing improvement over 12 months, though RT patients demonstrated a delayed recovery [59]. R. Prabhu et al. (2014) found that adding PCV chemotherapy to RT for WHO grade 2 glioma did not increase MMSE

decline; both arms showed mean MMSE improvement [49]. Similarly, Meihua Wang et al. (2010) found no between-arm difference in MMSE or QOL scores over 5 years in anaplastic oligodendroglioma treated with RT versus RT plus PCV, though scores declined in the last year of life for those who died [57].

In contrast, studies of high-grade glioma show more pronounced cognitive consequences. Prashasti Sharma et al. (2023) found that 56.6% of HGG patients developed cognitive impairment (mean MMSE 28.92→22.96) during follow-up, with tumor progression a key driver (66.7% of progressing patients vs. 28.6% stable patients) [56]. I. Rydén et al. (2025) found that one year after guideline-based treatment of IDH-mutant glioma, cognitive declines occurred in executive function (24%), learning/memory (23%), and language (21%), with chemoradiotherapy and older age as independent predictors [63].

G. Puglisi et al. (2025) demonstrated hemisphere-specific neurocognitive vulnerability in 200 high-grade glioma patients: left-hemisphere irradiation produced selective impairment in language measures (naming, token test, fluency), while right-hemisphere irradiation produced attentional and executive dysfunction; greatest declines were observed at 1 month post-treatment, with gradual recovery evident from 3 months [19]. Praxis was impaired in both hemispheres [19]. This hemisphere-specificity has practical implications for sparing strategies.

For GBM specifically, neither proton therapy nor IMRT demonstrated a significant advantage in cognitive preservation in two randomized trials. P. Brown et al. (2021) found no significant difference in time to cognitive failure between proton RT and IMRT (HR 0.88, 95% CI 0.45–1.75, $p=0.74$), though proton RT reduced grade ≥ 2 toxicity and fatigue [22]. Unexpectedly, C. Chung et al. (2017) found that IMPT was associated with shorter time to cognitive failure compared with IMRT in GBM (cumulative incidence at 4 months 59.3% vs. 37.2%), though this was hypothesized to reflect differences in survival and follow-up duration rather than a true cognitive harm from proton therapy [23].

In long-surviving patients with IDH-mutant glioma treated with proton beam therapy, D. M. J. Pelak et al. (2025) observed no significant decline in most cognitive scales over a median 62.5

months of follow-up, with verbal fluency (COWA) showing significant longitudinal improvement ($\beta=0.07$, $p<0.001$) [24].

Dose-Response Relationships and Critical Brain Structures

A consistent finding across neuroimaging-coupled studies is that radiation dose to specific brain structures mediates cognitive outcomes in a structure-dependent fashion. The hippocampus is the most extensively studied structure: F. Yang et al. (2022) found that mean left hippocampal dose was significantly associated with post-RT MMSE decline in GBM patients ($p=0.005$), while right hippocampal dose did not reach significance ($p=0.277$) [9]. R. Farjam et al. (2015) demonstrated that early hippocampal vascular changes (elevated K-trans) predicted late memory decline, with the effect most pronounced in older females ($r=-0.95$ with memory at 6 months, $p=0.0006$; $r=-0.88$ at 18 months, $p=0.02$) [10]. P. Pospíšil et al. (2017) showed that WBRT produced 12.9% and 12.0% decreases in right and left hippocampal N-acetylaspartate concentrations respectively at 4 months, correlating with memory decline [65]. The COG-SRS trial established that SRS dose constraints of ≤ 8.4 Gy (Dmax) to hippocampus and ≤ 12 Gy to white matter tracts allowed preservation of cognitive function, while inability to meet these constraints was associated with greater memory decline ($p=0.02$) [14, 14].

Beyond the hippocampus, multiple additional structures have been implicated. J. Yu et al. (2021) found that radiation dose to the right entorhinal cortex produced significant volume atrophy ($p<0.0001$), and left entorhinal cortical atrophy independently predicted worse total and delayed verbal memory (HVL-T-Total $p=0.002$, HVL-T-Delayed $p=0.023$) [12]. K. Tringale et al. (2017) showed that increased mean dose to left entorhinal and temporal pole white matter was associated with verbal memory decline ($r=-0.54$ for delayed recall, $p=0.02$ for both) [13], and that white matter microstructural changes—not hippocampal volume per se—were the primary imaging correlate of memory decline [13]. Prerana Baruah et al. (2025) found that corpus callosum dose was the strongest structural correlate of cognitive decline (mean 35.91 Gy in declining patients vs. 30.70 Gy in stable patients), though statistical significance was not reached, highlighting the corpus callosum as a candidate structure for future dose constraints [53, 53].

S. Gudipati et al. (2022) demonstrated that microstructural injury to thalamic nuclei was dose-dependent and progressive over 12 months: decreased volume in anterior, ventral, intralaminar, and medial thalamic fields predicted worse attention (WAIS-IV Digit Span Forward), while decreased FA in anterior fields predicted worse executive function (DKEFS Letter Fluency, $p=0.013-0.048$), and increased MD in posterior fields predicted worse visuospatial memory (BVMPT, $p=0.011-0.022$) [11, 11]. K. Redmond et al. (2015) found that higher mean RT dose to bilateral subventricular zones was associated with greater deterioration in processing speed at 6–12 months ($p=0.03$) in GBM patients, despite attempts at NPC-niche sparing [29, 29]. S. Hardy et al. (2020) identified that radiation dose to the amygdala correlated with increases in subjective depressive symptoms (left: $\rho=0.50$, $p=0.035$; right: $\rho=0.48$, $p=0.044$), representing a distinct emotional-cognitive vulnerability beyond memory circuits [48, 48].

C. Hahn et al. (2005) used FDG-PET to demonstrate that brain regions receiving >40 Gy showed 2–6% reductions in FDG uptake at both 3 weeks and 6 months post-RT, with decreased metabolic activity correlating with worse Wisconsin Card Sorting Test performance (average T-score decrease of 11, $p=0.037$) [31, 31].

Mean brain dose—the dose received by uninvolved brain parenchyma—emerges as a clinically actionable global metric. J. Jaspers et al. (2024) found that mean brain dose (average 17.8 Gy) inversely predicted 4 of 5 cognitive test scores in IDH-mutant glioma patients ($p<0.02$), independent of tumor grade [8]. J. Jaspers et al. (2025) confirmed this in the same cohort longitudinally [6]. Jianpeng Ma et al. (2024) found that high-dose RT (>30 Gy) produced worse MMSE scores, worse role functioning, and worsened depression at months 1–3 compared with low-dose RT [33].

Biological Mechanisms of Radiotherapy-Induced Cognitive Dysfunction

The mechanistic underpinnings of RT-induced cognitive impairment involve multiple interacting pathways. Vascular injury is an early and prominent mechanism: R. Farjam et al. (2015) demonstrated that RT increases hippocampal blood-brain barrier permeability (K-trans elevation from pre-RT to 1-month post-RT, $p<0.0004$), which then predicts late memory dysfunction [10]. C. Hahn et al. (2005) showed early (3-week) increases in relative regional blood flow in brain

receiving >30 Gy followed by subsequent reductions, alongside sustained metabolic depression [31].

White matter injury is the most frequently cited mechanistic pathway across the literature, implicated by both imaging and clinical studies [4, 11, 13, 15, 25, 42, 50, 59, 62, 68, 75, 76, 79]. M. van der Meulen et al. (2021) found small but significant inverse correlations between neurocognitive scores and white matter abnormalities (regression coefficients -0.048 to -0.347) and cerebral atrophy (-0.212 to -1.774) over 2 years in PCNSL patients [42]. K. Tringale et al. (2017) demonstrated that it was white matter microstructural changes—increased mean diffusivity and fractional anisotropy in parahippocampal white matter—rather than hippocampal volume loss that best predicted verbal memory decline [13]. Xuyun Xie et al. (2023) applied diffusion kurtosis imaging to identify 28 regions with microstructural alterations after WBRT, of which 9 correlated with cognitive decline [62].

Neuronal loss and suppression of neurogenesis represent complementary mechanisms, particularly in the hippocampal dentate gyrus. P. Pospíšil et al. (2017) directly measured hippocampal N-acetylaspartate—a neuronal marker—and found 12–13% reductions bilaterally after WBRT, correlating with memory performance [65]. Shinn-yn Lin et al. (2015) invoked impaired hippocampal neurogenesis as the mechanistic rationale for hippocampal sparing [78]. S. Hardy et al. (2023) described dose-dependent cortical, hippocampal, and amygdalar atrophy alongside reduced neural stem cell pools as core mechanisms of RT-induced cognitive decline [50].

Neuroinflammation represents a third key mechanism. Jianpeng Ma et al. (2024) described activation of microglia and astrocytes producing pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-18) along with endothelial exhaustion and inhibition of neurogenesis following irradiation [33]. C. Armstrong et al. (2012) noted that immune-mediated inflammatory processes were associated with early-delayed memory impairment, and cited oxidative stress alongside downregulation of hippocampal neurogenesis as contributing mechanisms [25]. J. Kirkpatrick et al. (2020) tested the hypothesis that oxidative stress is a primary driver by investigating BMX-001, a superoxide dismutase mimetic, as a neuroprotectant in patients with numerous brain metastases receiving WBRT [30]. K. Peters et al. (2022) found that most GBM patients treated with BMX-001 during

RT and temozolomide showed stable or improved neurocognitive function at 2 and 6 months post-RT [77].

Kristin M. Huntoon et al. (2022) demonstrated a molecular mechanism in the apolipoprotein pathway: patients with low baseline serum levels of ApoJ, ApoE, or ApoA ($p < 0.01$) and higher amyloid beta ($A\beta_{1-42}$) levels ($p = 0.048$) were significantly more likely to experience cognitive decline at 3 months post-SRS, while lower ApoJ was associated with cognitive decline after WBRT [61]. This ApoJ- $A\beta$ interaction suggests a protein aggregation/clearance pathway analogous to Alzheimer's disease pathophysiology, potentially explaining individual variation in cognitive susceptibility [61].

Risk Factors Modifying Cognitive Vulnerability

Older age consistently emerges as a key risk factor for RT-induced cognitive impairment. M. Chan et al. (2020) showed that every additional year of age conferred an OR of 1.12 ($p < 0.01$) for cognitive decline after WBRT [15]. Toshimichi Nakano et al. (2018) found that patients aged ≥ 65 years had significantly worse total recall ($p = 0.01$) and delayed recognition ($p = 0.02$) at 4 months post-WBRT compared with younger patients [16]. Assaf Berger et al. (2018) observed that patients under 60 years showed cognitive improvements after SRS while those aged ≥ 60 showed no significant change [58]. R. Farjam et al. (2015) identified that hippocampal vascular dose response was most pronounced in older females, with memory correlations significant in that subgroup [10].

Baseline cognitive reserve and education level modulate cognitive outcomes. J. Yu et al. (2021) found that higher educational attainment was associated with less memory decline over 12 months ($p = 0.01$) [12]. C. Cramer et al. (2018) found that less education, poorer performance status, lower household income, and not being employed outside the home were all associated with higher likelihood of meeting MCI criteria post-RT [74]. S. Rapp et al. (2015) found that the cognitive benefits of donepezil were greater for those with greater pretreatment cognitive impairment [17], a finding corroborated by M. Naughton et al. (2018), who showed that donepezil improved HRQL in those with more baseline symptoms while producing worse functional well-being in those with fewer baseline symptoms [21].

Pre-existing white matter disease dramatically amplifies WBRT toxicity. M. Chan et al. (2020) found that a Fazekas score ≥ 3 conferred an OR of 6.4 ($p < 0.01$) for cognitive decline, and all patients with severe leukoencephalopathy (Fazekas=6/6) required institutionalization or full-time nursing support [15].

Tumor characteristics also modify cognitive risk. Prashasti Sharma et al. (2023) found that WHO grade 4, IDH-wild type status, and poor RPA class were univariately associated with cognitive impairment, though PTV size and ipsilateral hippocampal dose were independently significant on multivariate analysis [56]. G. Puglisi et al. (2025) identified irradiated hemisphere as a determinant of the cognitive domain affected, with left-sided treatment producing language deficits and right-sided treatment producing attentional/executive deficits [19].

Depression and anxiety symptoms independently predict cognitive decline in patients undergoing brain RT, as demonstrated by M. Tibbs et al. (2019) in a 54-patient prospective trial: higher anxiety on the Beck Anxiety Inventory independently predicted decline in attention/processing speed across three DKEFS-TMT subtests ($p < 0.001$ – 0.011 on multivariable analysis), and higher depression predicted Letter Sequencing decline ($p = 0.013$) [18]. Health-related QOL dimensions similarly predict neurocognitive outcomes independently of mood, as shown by M. Salans et al. (2020, 2021) [27, 52]. These bidirectional relationships complicate attribution of cognitive effects to RT alone.

Gender differences have been noted in several studies: R. Farjam et al. (2015) found the hippocampal vascular response to RT was more pronounced in females [10], and A. Tooze & J. Sheehan (2018) found male pituitary adenoma patients were more likely to demonstrate anterograde memory impairments than female patients (immediate: $t = -3.41$, $p = 0.003$; delayed: $t = -3.80$, $p = 0.001$) [46].

Temporal Patterns of Cognitive Change

The temporal evolution of RT-induced cognitive change follows recognizable phases. Acute effects during or immediately after treatment—including transient increases in regional cerebral blood flow and somnolence syndrome—were documented by C. Hahn et al. (2005) [31] and M. Chan et al. (2020) [15]. Early delayed effects, typically at 1–4 months, constitute the most clinically

prominent phase: G. Puglisi et al. (2025) found the greatest decline across all domains at 1 month post-chemoRT, with gradual recovery from 3 months [19]. C. Armstrong et al. (2012) observed a decline in semantic memory retrieval by 6 weeks post-RT with recovery by 1 year in low-grade tumor patients [25]. A. Tallet et al. (2012) established that cognitive decline peaks at 4 months after WBRT [3].

For WBRT specifically, cognitive deterioration may be progressive when brain metastasis control is poor, but can stabilize or partially recover when disease is controlled—consistent with the finding of E. V. van Grinsven et al. (2021) that WBRT patients with survival ≥ 9 –15 months show stabilization or return toward baseline [4]. In contrast, SRS-related cognitive effects are largely transient [4].

Late delayed effects, defined as occurring months to years after RT, are best documented in long-term survivors. T. Lawrie et al. (2019) found that the relative risk of cognitive impairment in low-grade glioma patients treated with RT increased with time, reaching RR 1.95 (95% CI 1.02–3.71) at 12-year follow-up [32]. K. Edelstein et al. (2014) documented progressive cognitive changes over up to 6.77 years post-RT in primary brain tumor patients [75]. In IDH-mutant glioma, J. Jaspers et al. (2025) observed no time-related decline over a median 5.8 years, though the mean brain dose relationship suggests cumulative dose effects that operate over this extended timeframe [6].

Prevention and Mitigation Strategies

Several intervention strategies to attenuate RT-induced cognitive impairment have been tested with variable success. Hippocampal avoidance WBRT is the most robustly supported technique, with multiple prospective and retrospective studies demonstrating preserved cognitive function without compromising tumor control or survival [20, 67, 70, 76, 78]. The connectivity-informed cognitive-sparing SRS approach (Connor Puett et al., 2025) extends this paradigm to 23 white matter tracts and represents a promising advance for metastatic patients [14].

Memantine, an NMDA receptor antagonist, reduces cognitive failure rates when combined with WBRT (summary cognitive failure rate 43.7% vs. 53.2% for WBRT alone in the meta-analysis) [2]. Combining memantine with hippocampal avoidance provides additive benefit

(adjusted HR=0.74) [20]. However, N. Laack et al. (2018) noted that while objective cognitive function declined over time on WBRT with memantine, no HRQOL differences between arms were detected, suggesting a disconnect between objective and subjective cognitive measures [60].

Donepezil (acetylcholinesterase inhibitor) produced modest but statistically significant improvements in memory recognition ($p=0.027$), discrimination ($p=0.007$), and motor speed ($p=0.016$) in post-irradiation brain tumor survivors in the phase III trial by S. Rapp et al. (2015), though the primary composite cognitive outcome did not differ [17]. Benefit was concentrated in patients with greater pretreatment impairment, as confirmed by M. Naughton et al. (2018) [21]. Neither armodafinil [47, 72] nor d-threo-methylphenidate [38] demonstrated significant cognitive or fatigue benefit in phase II–III trials of brain tumor patients undergoing RT.

BMX-001, the superoxide dismutase mimetic, showed promising results in a phase I trial (K. Peters et al., 2022), with most GBM patients demonstrating stable or improved cognitive function at 2 and 6 months post-concurrent RT/TMZ [77]. A randomized phase II trial was subsequently opened [30]. Reduced-dose WBRT regimens in PCNSL (B. Fisher et al., 2005) delayed leukoencephalopathy without eliminating it [37], and delaying or avoiding WBRT entirely in PCNSL preserved QOL and cognition at the cost of inferior intracranial control in some series [54, 68].

Proton beam therapy has theoretical advantages due to reduced integral dose to uninvolved brain. D. M. J. Pelak et al. (2025) showed stable long-term cognition with PBT in IDH-mutant glioma, with verbal fluency improving over time [24]. However, the two randomized trials comparing proton and photon RT in GBM (P. Brown et al., 2021; C. Chung et al., 2017) found no advantage in time to cognitive failure for proton RT, though both trials had significant limitations including short follow-up relative to GBM prognosis and differential survival that complicates cognitive comparisons [22, 23].

Synthesis

The Central Tension: WBRT vs. Focal Approaches

The most prominent apparent contradiction in this literature is between two legitimate clinical goals: maximal intracranial tumor control and cognitive preservation. Multiple RCTs

confirm that WBRT adds tumor control compared with SRS alone—intracranial control at 12 months was 89.5% vs. 20% (SRS alone) in P. Brown et al. (2016) [1], and 81.5% vs. 40.7% in J. Palmer et al. (2022) [26] —yet this superior control is achieved at the cost of severe cognitive morbidity (91.7% vs. 63.5% cognitive deterioration at 3 months [1]). Since overall survival does not differ between WBRT and SRS-alone strategies in randomized trials [1, 26], the evidence supports SRS-alone for patients with 1–3 brain metastases amenable to radiosurgery. However, the finding of H. Aoyama et al. (2007) that SRS-alone patients experience cognitive deterioration earlier (mean 7.6 months to MMSE drop vs. 16.5 months with WBRT) [34] indicates that intracranial progression after SRS-alone is itself a driver of cognitive decline—suggesting that the benefit of SRS on cognition is partly mediated through preservation of cognitive reserve rather than through avoiding radiation toxicity per se.

Distinguishing Tumor-Related from Treatment-Related Cognitive Effects

A critical methodological challenge pervades this literature. The high baseline prevalence of cognitive impairment—91% in WBRT candidates [4], 90% in PCNSL patients [42], and 66% meeting MCI criteria post-RT [74] —reflects the disease burden itself. In the Aoyama et al. (2007) trial, baseline MMSE was significantly correlated with tumor volume, edema, age, and performance status [34], demonstrating that the tumor microenvironment independently degrades cognition before any treatment. Studies that account for this through prospective baseline measurement, reliable change indices correcting for practice effects [12–14], and exclusion of patients with progressive disease [59] are better positioned to isolate treatment-specific effects. Studies relying solely on the MMSE [9, 34, 37, 44, 49, 54, 56, 57, 71] are likely to miss subtle treatment-related impairments, as noted by multiple authors [49, 57].

Explaining the Apparent Stability of Cognition in Some Glioma Studies

Several studies in low-grade and IDH-mutant glioma found stable or even improving cognitive function despite RT [5–7, 49, 57]. This stands in apparent contrast to evidence that RT causes white matter damage, hippocampal neuronal loss, and thalamic atrophy. The explanation likely reflects several interacting factors. First, patients with low-grade or IDH-mutant gliomas typically receive partial brain RT with relative sparing of uninvolved structures, and mean brain

doses of approximately 17–18 Gy [6, 8] are substantially lower than those associated with cognitive toxicity in WBRT. Second, the disease in this population is slow-growing, and successful tumor control may itself stabilize cognition that was progressively declining due to tumor infiltration. Third, the populations in these studies were younger (e.g., median age 41–50 years) [12, 24], better-educated, and had higher baseline cognitive reserve, all of which are protective. Fourth, practice effects from repeated neuropsychological testing can mask modest declines, though studies using reliable change indices account for this [6, 8, 12]. When dose-response analysis is performed within these populations, mean brain dose consistently predicts cognitive trajectories even when group-level scores appear stable [6, 8], suggesting that individual patients receiving higher brain doses experience decline that is masked at the group level.

Dose-Structure-Cognition Specificity

Multiple studies converge on a consistent dose-response framework in which specific brain structures mediate specific cognitive domains. The hippocampus mediates verbal and spatial memory [9, 10, 33, 70, 76, 78]; the entorhinal cortex mediates verbal memory (left-sided) and shows dose-dependent atrophy [12, 13]; the thalamus and its nuclei mediate attention, executive function, and visuospatial memory [11]; the subventricular zone mediates processing speed [29]; the amygdala mediates emotional processing and mood [48]; and white matter tracts throughout the medial temporal lobe and corpus callosum mediate verbal memory and processing speed [13, 50, 53]. This specificity provides an anatomical framework for designing patient-specific dose constraints: rather than a single organ-at-risk, the brain has a distributed set of structures each with domain-specific importance that should be contoured and constrained according to the patient's pretreatment cognitive profile and priorities.

The COG-SRS trial (Connor Puett et al., 2025) demonstrated that incorporating 23 white matter tracts as organs-at-risk in SRS treatment planning, with evidence-based dose constraints, eliminated overall cognitive decline at 3 months—a result not achieved in any prior SRS trial—while maintaining local control [14]. The patients whose tumor locations prevented meeting WMT constraints showed significantly more memory decline ($p=0.02$) [14], confirming the causal role of

white matter tract dose in cognitive outcomes and establishing that the constraint thresholds ($D_{max} \leq 12$ Gy for WMT, ≤ 8.4 Gy for hippocampus in single-fraction SRS) are clinically meaningful.

Conclusions for Specific Clinical Contexts

For patients with brain metastases amenable to SRS: SRS alone preserves cognitive function substantially better than SRS plus WBRT [1, 26], with no overall survival disadvantage. When WBRT is clinically necessary, hippocampal avoidance significantly reduces cognitive failure rates [20, 67], and memantine provides additive neuroprotection [20]. Patients with pre-existing leukoencephalopathy (Fazekas ≥ 3) face dramatically elevated cognitive risk from WBRT and should be counseled accordingly or offered alternative strategies [15]. For patients with numerous brain metastases (>10) where SRS is less feasible, the emerging evidence that GKRS is feasible even for 11–20 metastases with superior cognitive preservation warrants continued trial investigation [28].

For primary brain tumor patients: cognitive morbidity is multifactorial, with the tumor itself contributing substantially at baseline [25, 42]. Partial brain RT with modern conformal techniques in well-controlled disease appears relatively cognitively safe over the medium term [5–7], though mean brain dose should be minimized as it predicts individual cognitive trajectories [6, 8]. Older patients and those receiving chemoradiotherapy face the greatest cognitive risk [56, 63]. The domain-specificity of cognitive vulnerability based on irradiated hemisphere [19] and specific structures argues for individualized neuropsychological monitoring and pretreatment baseline assessment as standard components of care across all primary brain tumor RT protocols [55, 56].

DISCUSSION

This systematic review of 80 studies provides a comprehensive and detailed synthesis of the relationship between radiotherapy and cognitive impairment in brain tumor patients. The findings consistently demonstrate that while RT is effective for tumor control, it carries a significant risk of cognitive toxicity, the magnitude of which varies substantially by modality, dose distribution, and patient-specific vulnerability.

Hierarchy of Cognitive Toxicity Across Radiotherapy Modalities

The most prominent and clinically relevant finding is a clear hierarchy of cognitive toxicity: WBRT produces the most severe and prevalent cognitive decline, followed by SRS, while focal or partial brain RT for primary brain tumors appears relatively cognitively sparing over the medium term. In the landmark randomized trial by P. Brown et al. (2016), cognitive deterioration at 3 months occurred in 91.7% of patients receiving SRS+WBRT compared to 63.5% with SRS alone (difference -28.2%, $p < 0.001$). This finding was corroborated by Palmer et al. (2022), who showed that 70% of WBRT recipients declined by ≥ 2 SD on at least one cognitive test versus only 22% in the SRS arm. The meta-analysis by Lehrer et al. (2019) quantified cognitive failure rates at 3-4 months: WBRT 53.2%, SRS 20.9%, WBRT+memantine 43.7%, and HA-WBRT 33.3%. These data establish that SRS alone is the cognitive-sparing standard for patients with 1-3 brain metastases amenable to radiosurgery, a conclusion reinforced by no overall survival disadvantage in randomized trials (P. Brown et al., 2016; Aoyama et al., 2007).

The Central Tension: Tumor Control Versus Cognitive Preservation

An apparent contradiction emerges from the data: while WBRT significantly improves intracranial tumor control compared to SRS alone—12-month control 89.5% vs. 20% in P. Brown et al. (2016)—this superior control is achieved at the cost of substantial cognitive morbidity. However, the finding by Aoyama et al. (2007) that SRS-alone patients experienced earlier cognitive deterioration (mean 7.6 months to MMSE drop vs. 16.5 months with WBRT) demonstrates that intracranial progression itself is a powerful driver of cognitive decline. Thus, the cognitive benefit of SRS is partly mediated through preservation of cognitive reserve by avoiding radiation toxicity, yet this benefit can be eroded by subsequent tumor progression. This tension mandates a personalized approach: SRS alone is preferred for patients with limited metastases and good prognosis, but WBRT may still be considered when micrometastatic disease is suspected or when SRS is technically infeasible, provided hippocampal avoidance and memantine are employed to mitigate toxicity (Crockett & Simões, 2023).

Distinguishing Tumor-Related from Treatment-Related Cognitive Effects

A critical methodological challenge pervading this literature is the high baseline prevalence of cognitive impairment, driven by the tumor itself. Van Grinsven et al. (2021) reported that 91% of

brain metastasis patients scheduled for WBRT already showed cognitive deficits; similarly, 90% of PCNSL patients had impairments before any treatment (van der Meulen et al., 2021). In the Aoyama et al. (2007) trial, baseline MMSE correlated with tumor volume, edema, age, and performance status. Therefore, studies failing to account for baseline function through prospective repeated measures and reliable change indices (RCIs) may over- or under-estimate treatment-specific effects. Studies employing RCIs, such as Yu et al. (2021) and Puett et al. (2025), are better positioned to isolate true treatment-related decline from disease effects or practice effects.

Explaining Apparent Cognitive Stability in Low-Grade and IDH-Mutant Glioma

Several prospective studies in LGG and IDH-mutant glioma found stable or even improving cognitive function despite RT (Laack et al., 2005; Rydelius et al., 2020; Jaspers et al., 2025). This finding stands in contrast to the severe declines seen with WBRT. The explanation is multifactorial. First, partial brain RT delivers substantially lower mean brain doses (approximately 17-18 Gy) compared to WBRT (Jaspers et al., 2024). Second, successful tumor control may stabilize cognition that was progressively declining due to tumor infiltration. Third, these populations are typically younger (median 41-50 years), better educated, and have higher baseline cognitive reserve, all of which are protective (Yu et al., 2021; Cramer et al., 2018). Fourth, practice effects can mask modest declines; however, when dose-response analysis is performed within these cohorts—even when group-level scores appear stable—mean brain dose consistently and inversely predicts individual cognitive trajectories (Jaspers et al., 2024; Jaspers et al., 2025). This indicates that some patients receiving higher brain doses do experience decline that is obscured at the group level.

Dose-Response Relationships and Critical Brain Structures

A major advance in the field is the elucidation of dose-structure-cognition specificity. Multiple studies converge on a framework where specific brain structures mediate specific cognitive domains. The hippocampus is the most extensively studied: Yang et al. (2022) found that mean left hippocampal dose was significantly associated with post-RT MMSE decline ($p=0.005$); Farjam et al. (2015) demonstrated that early hippocampal vascular changes (elevated K-trans) predicted late memory decline, especially in older females ($r=-0.95$ at 6 months); and Pospíšil et al. (2017) showed that WBRT produced 12-13% reductions in hippocampal N-acetylaspartate (a

neuronal marker) correlating with memory loss. The entorhinal cortex also plays a critical role: Yu et al. (2021) showed that radiation dose to the right entorhinal cortex produced significant atrophy ($p < 0.0001$), with left entorhinal atrophy independently predicting worse verbal memory. Tringale et al. (2017) further demonstrated that white matter microstructural changes in the parahippocampal region—not hippocampal volume per se—were the primary imaging correlate of memory decline.

Beyond mesial temporal structures, the thalamus and subventricular zone are implicated. Gudipati et al. (2022) demonstrated that dose-dependent microstructural injury to thalamic nuclei predicted worse attention (anterior fields) and executive function (anterior fields), while posterior thalamic injury predicted visuospatial memory impairment. Redmond et al. (2015) found that higher mean RT dose to bilateral subventricular zones was associated with greater deterioration in processing speed at 6-12 months ($p = 0.03$). The COG-SRS trial (Puett et al., 2025) established clinically meaningful dose constraints: $D_{max} \leq 12$ Gy for white matter tracts and ≤ 8.4 Gy for hippocampus in single-fraction SRS, with inability to meet these constraints resulting in significantly greater memory decline ($p = 0.02$). Similarly, Baruah et al. (2025) identified corpus callosum dose as a candidate structural correlate of cognitive decline (mean 35.91 Gy in decliners vs. 30.70 Gy in stable patients). Finally, mean brain dose emerges as a clinically actionable global metric: Jaspers et al. (2024) found that mean brain dose (average 17.8 Gy) inversely predicted 4 of 5 cognitive test scores in IDH-mutant glioma ($p < 0.02$). These data collectively argue for moving from a single organ-at-risk (hippocampus) to a distributed set of constraints tailored to the patient's pretreatment cognitive profile.

Biological Mechanisms

The biological underpinnings of radiation-induced cognitive dysfunction are multifaceted. Vascular injury is an early and prominent mechanism. Farjam et al. (2015) demonstrated that RT increases hippocampal blood-brain barrier permeability (K-trans elevation from pre-RT to 1-month post-RT, $p < 0.0004$), which then predicts late memory dysfunction. Hahn et al. (2005) showed early (3-week) increases in regional cerebral blood flow in areas receiving > 30 Gy, followed by sustained metabolic depression on FDG-PET. White matter injury is the most frequently cited mechanistic pathway, implicated by multiple studies (van der Meulen et al., 2021; Xie et al., 2023; Tringale et

al., 2017). Tringale et al. (2017) specifically showed that increased mean diffusivity and fractional anisotropy in parahippocampal white matter, not hippocampal volume loss, best predicted verbal memory decline. Neuronal loss and suppressed neurogenesis are complementary mechanisms, particularly in the hippocampal dentate gyrus, as evidenced by reduced N-acetylaspartate (Pospíšil et al., 2017). Neuroinflammation—activation of microglia and astrocytes producing pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6)—is a third key mechanism (Ma et al., 2024; Armstrong et al., 2012). Oxidative stress is increasingly recognized as a primary driver; the superoxide dismutase mimetic BMX-001 showed promising neuroprotective effects, with most GBM patients demonstrating stable or improved cognitive function at 2 and 6 months post-RT (Peters et al., 2022). A novel molecular pathway was identified by Huntoon et al. (2022): low baseline serum levels of ApoJ, ApoE, or ApoA ($p < 0.01$) and higher amyloid beta (A β 1-42) levels ($p = 0.048$) were associated with cognitive decline post-SRS, suggesting a protein aggregation/clearance pathway analogous to Alzheimer's disease.

Risk Factors Modifying Vulnerability

Older age consistently emerges as a dominant risk factor. Chan et al. (2020) showed each additional year conferred an OR of 1.12 for cognitive decline after WBRT ($p < 0.01$); Nakano et al. (2018) found that patients ≥ 65 years had significantly worse memory outcomes; and Berger et al. (2018) observed that patients under 60 years showed cognitive improvements after SRS while older patients did not. Baseline cognitive reserve and education are protective: Yu et al. (2021) found higher education associated with less memory decline ($p = 0.01$), and Cramer et al. (2018) linked less education, poorer performance status, and lower income with higher likelihood of post-RT MCI. Pre-existing white matter disease dramatically amplifies risk: a Fazekas score ≥ 3 conferred an OR of 6.4 for cognitive decline, and all patients with severe leukoencephalopathy required institutionalization (Chan et al., 2020). Tumor characteristics also modify risk: WHO grade 4, IDH-wild type status, and poor RPA class were associated with cognitive impairment (Sharma et al., 2023), and hemisphere-specific effects were striking: left-sided irradiation produced language deficits while right-sided irradiation produced attentional/executive deficits (Puglisi et al., 2025). Depression and anxiety symptoms independently predict cognitive decline, with higher anxiety

predicting decline across multiple executive function subtests ($p < 0.001$ - 0.011) (Tibbs et al., 2019). Gender differences were noted by Farjam et al. (2015) (greater hippocampal vascular response in females) and Tooze & Sheehan (2018) (males more likely to have memory impairment after GKRS).

Temporal Patterns of Cognitive Change

The temporal evolution follows recognizable phases. Acute effects (during or immediately after RT) include transient increases in regional cerebral blood flow and somnolence syndrome (Hahn et al., 2005; Chan et al., 2020). Early delayed effects (1-4 months) constitute the most clinically prominent phase: Puglisi et al. (2025) found the greatest decline across all domains at 1 month post-chemoRT, with gradual recovery from 3 months; Armstrong et al. (2012) observed decline in semantic memory retrieval by 6 weeks with recovery by 1 year; and Tallet et al. (2012) established that cognitive decline peaks at 4 months after WBRT. For WBRT, deterioration may be progressive when brain metastasis control is poor but can stabilize or partially recover when disease is controlled (Van Grinsven et al., 2021). Late delayed effects (months to years) are best documented in long-term survivors: Lawrie et al. (2019) found the relative risk of cognitive impairment in LGG patients treated with RT reached RR 1.95 (95% CI 1.02-3.71) at 12-year follow-up; Edelstein et al. (2014) documented progressive cognitive changes over up to 6.77 years post-RT. In contrast, SRS-related cognitive effects are largely transient, with most patients returning to baseline within 5 months (Van Grinsven et al., 2021).

Prevention and Mitigation Strategies

Several intervention strategies have been tested. Hippocampal avoidance WBRT is the most robustly supported technique. The NRG CC001 trial (Crockett & Simões, 2023) randomized 518 patients to HA-WBRT+memantine vs. WBRT+memantine and demonstrated significantly reduced cognitive failure (adjusted HR=0.74, $p=0.016$), with younger patients (≤ 61 years) benefiting most (HR=0.61). Multiple other studies confirmed preserved cognitive function with HA-WBRT without compromising tumor control or survival (Shang et al., 2022; Wang et al., 2021; Lin et al., 2015; Leskinen et al., 2023). The connectivity-informed cognitive-sparing SRS approach (Puett et al., 2025) extends this paradigm to 23 white matter tracts and represents a promising advance.

Memantine alone reduces cognitive failure rates compared to WBRT alone (Lehrer et al., 2019), and combining memantine with HA provides additive benefit (Crockett & Simões, 2023). However, Laack et al. (2018) noted no HRQOL differences between memantine and placebo arms despite differences in objective cognition, suggesting a disconnect between objective and subjective measures. Donepezil produced modest but statistically significant improvements in memory recognition ($p=0.027$), discrimination ($p=0.007$), and motor speed ($p=0.016$) in post-irradiation survivors, though the primary composite outcome did not differ (Rapp et al., 2015; Naughton et al., 2018). Benefit was concentrated in patients with greater pretreatment impairment. Armodafinil (Page et al., 2015; Shaw et al., 2013) and d-threo-methylphenidate (Butler et al., 2007) showed no significant cognitive or fatigue benefit in phase II-III trials. BMX-001, a superoxide dismutase mimetic, showed promising phase I results with stable or improved cognition in most GBM patients (Peters et al., 2022), and a randomized phase II trial is underway (Kirkpatrick et al., 2020). Reduced-dose or delayed WBRT in PCNSL preserves cognition at the cost of inferior control in some series (Herrlinger et al., 2017; Fisher et al., 2005; Correa, 2021). Proton beam therapy has theoretical advantages, but two randomized trials in GBM found no advantage in time to cognitive failure for proton vs. photon RT, though both trials had significant limitations (P. Brown et al., 2021; Chung et al., 2017). In contrast, Pelak et al. (2025) showed stable long-term cognition with proton beam therapy in IDH-mutant glioma.

Clinical Recommendations

Based on the synthesized evidence, the following clinical recommendations are offered. For patients with 1-3 brain metastases amenable to SRS, SRS alone is the standard of care to preserve cognitive function (P. Brown et al., 2016; Palmer et al., 2022). When WBRT is necessary, hippocampal avoidance should be strongly considered (Crockett & Simões, 2023; Leskinen et al., 2023), and memantine should be added (Lehrer et al., 2019). Patients with severe pre-existing leukoencephalopathy (Fazekas ≥ 3) face dramatically elevated risk and should be counseled accordingly or offered alternative strategies (Chan et al., 2020). For primary brain tumors, partial brain RT with modern conformal techniques is relatively safe, but mean brain dose should be minimized to <18 Gy when feasible (Jaspers et al., 2024). Dosimetric constraints should include:

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hippocampus $D_{max} \leq 8.4$ Gy (single-fraction SRS) or mean dose ≤ 16 Gy (fractionated), white matter tract $D_{max} \leq 12$ Gy, and consideration of entorhinal cortex and corpus callosum constraints (Puett et al., 2025; Yu et al., 2021; Baruah et al., 2025). Baseline neuropsychological assessment should be standard, followed by domain-specific monitoring at 3, 6, and 12 months post-RT. Donepezil may be considered for post-irradiation survivors with established cognitive impairment, particularly memory deficits (Rapp et al., 2015).

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 80 studies demonstrates that radiotherapy for brain tumors is associated with a significant risk of cognitive impairment, but the magnitude of this risk is highly dependent on modality, dose distribution, and patient factors. WBRT produces the most severe and prevalent cognitive decline, particularly in memory and processing speed, while SRS and focal RT are substantially less toxic. Hippocampal avoidance and memantine provide additive neuroprotection in the WBRT setting. Dose-response relationships are structure-specific, with the hippocampus, entorhinal cortex, thalamus, white matter tracts, and mean brain dose all independently predicting cognitive trajectories. Biological mechanisms include vascular injury, white matter damage, neuroinflammation, and oxidative stress. Key risk factors are older age, low cognitive reserve, pre-existing leukoencephalopathy, and mood disorders. Neuroprotective strategies with proven benefit include hippocampal avoidance and memantine, while donepezil offers modest benefit in selected patients.

Recommendations

For clinical practice: (1) In patients with 1-3 brain metastases, SRS alone should be the standard of care. (2) When WBRT is unavoidable, hippocampal avoidance and memantine should be employed. (3) Baseline and serial neurocognitive assessments should be integrated into routine care. (4) Dosimetric constraints should be applied to multiple brain structures, not just the hippocampus. For future research: (1) Randomized trials should incorporate cognitive endpoints as primary outcomes. (2) Validated reliable change indices should be standard to separate treatment

effects from disease and practice effects. (3) Longer follow-up (≥ 5 years) is needed to characterize late delayed effects. (4) The role of emerging agents like BMX-001 requires phase III validation. (5) Individualized dose constraints for distributed brain structures should be prospectively validated. (6) Studies should stratify by molecular subtype (e.g., IDH mutation status) given differential vulnerability.

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