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Mitigating radiation-induced cognitive toxicity in brain metastases: More questions than answers

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Abstract

The emergence of advanced systemic therapies added to the use of cranial radiation techniques has significantly improved outcomes for cancer patients with multiple brain metastases (BM), leading to a considerable increase in long-term survivors. In this context, the rise of radiation-induced cognitive toxicity (RICT) has become increasingly relevant. In this critical narrative review, we address the controversies arising from clinical trials aimed at mitigating RICT. We thoroughly examine interventions such as memantine, hippocampal avoidance irradiation during BM treatment or in a prophylactic setting, and the assessment of cognitive safety in stereotactic radiosurgery (SRS). Our focus extends to recent neuroscience research findings, emphasizing the importance of preserving not only the hippocampal cortex but also other cortical regions involved in neural dynamic networks and their intricate role in encoding new memories. Despite treatment advancements, effectively managing patients with multiple BM and determining the optimal timing and integration of radiation and systemic treatments remain areas requiring further elucidation. Future trials are required to delineate optimal indications and ensure SRS safety. Additionally, the impact of new systemic therapies and the potential effects of delaying irradiation on cognitive functioning also need to be addressed. Inclusive trial designs, encompassing patients with multiple BM and accounting for diverse treatment scenarios, are essential for advancing effective strategies in managing RICT and the treatment of BM patients.

Key Points

- Although phase 3 trials suggest a favorable impact of memantine use and hippocampal avoidance irradiation in mitigating radiation-induced cognitive toxicity, these trials raise concerns that warrant thorough discussion before full acceptance.
- Hippocampal sparing irradiation relies on a hypothesis that is increasingly controversial and likely insufficient to mitigate the extensive brain damage associated with radiation-induced cognitive toxicity.
- Cognitive safety of stereotactic radiosurgery for multiple brain metastases, balancing efficacy and safety, is still not well defined.

Radiotherapy is a crucial part of cancer treatment, used alongside surgery, cytostatic drugs, and emerging strategies like targeted therapies and immunotherapy. However, when dealing with brain metastases (BM), radiotherapy, while effective for limited cerebral metastatic disease, can have medium- and long-term adverse effects impacting patients' quality of life and cognitive abilities.[1]

Radiation-induced cognitive toxicity (RICT), although common, is not exclusively associated with whole-brain radiotherapy (WBRT). It primarily affects attention and short-term

memory, leading to moderate to severe impairment in verbal memory and executive functions. While some patients show stability over time, others may progress to subcortical dementia characterized by gait alterations, apathy, and extrapyramidal symptoms.[2] Advanced imaging techniques have revealed reductions in cortical thickness in key brain structures such as the hippocampus and basal ganglia.[3–5] Additionally, more extensive white matter damage has been observed, particularly affecting the fornix, cingulate, and corpus callosum.[5,6]

Preclinical research has identified several mechanisms underlying radiation-induced cognitive decline. These include reduced proliferation and altered differentiation of neural precursors in the hippocampus, an inflammatory response triggered by oxidative damage, changes in microvasculature, alterations in dendritic morphology of mature neurons, impaired physiological function of mature hippocampal neurons, and persistent activation of microglia.[1,7,8]

Over the last decade, cognitive toxicity has become more relevant, driven by the emergence of novel and more effective systemic therapies that led to a considerable increase in long-term survivors. Despite these therapeutic advancements, effectively managing patients with multiple BM and determining the optimal timing and integration of radiation and systemic treatments remain complex issues. Nevertheless, recent clinical trials that focused on preventing RICT, through interventions such as memantine, hippocampal radiotherapy avoidance (HA), or stereotactic radiosurgery (SRS) instead of WBRT have reported promising results. The objective of this critical narrative review is to contextualize the significance and conceptualization of the results obtained from these seminal phase 3 studies. Additionally, we reviewed and referenced other studies to provide a comprehensive understanding of the context that led to the development of the analyzed phase 3 trials.

Memantine Neuroprotection

One of the proposed mechanisms underlying RICT involves an increase in glutamate levels and the overstimulation of N-methyl-D-aspartate receptors (NMDARs). NMDARs play a critical role in maintaining synaptic plasticity, a mechanism essential for memory and learning.[9,10] This mechanism prompted interest in exploring memantine, an uncompetitive NMDAR antagonist, as a potential intervention to mitigate RICT. Notably, this investigation of memantine was based on the same pathophysiological mechanism that led to its approval for the treatment of moderate to severe Alzheimer's disease.[11]

In the phase 3 RTOG 0614 study, 508 patients with solid tumors and BM undergoing WBRT were randomized to receive memantine or placebo.[12] The authors observed a strong yet not statistically significant trend towards improvement in the primary endpoint (delayed recall verbal memory) among patients with WBRT who received memantine ($P = .0587$). There was significant improvement in the secondary endpoint, time to cognitive failure (TCF) at 6 months, favoring the memantine group (54% showed cognitive impairment compared with 65% in the placebo group). However, the substantial loss of patients during the trial (approximately 50%) may have impacted the internal validity of the study. Additional secondary cognitive endpoints, involving executive functions—often altered in the context of RICT—yielded inconsistent results.

While memantine is increasingly recognized as a standard treatment for patients receiving WBRT for BM, both in clinical practice and ongoing trials, discrepancies persist between American and European guidelines.[13,14]

There are questions and concerns regarding the interpretation of the results. Although patient groups were well-balanced at baseline in terms of variables potentially impacting cognition (excluding cardiovascular comorbidities that were not considered), the significant loss of patients prompts concerns about a potential bias of the evaluable cohort. Additionally, intracranial progression was not specifically considered in the assessment and interpretation of the primary cognitive outcome (delayed recall verbal memory); it was only included in the secondary endpoint (TCF). On the whole, while there is a correlation between cognitive decline and both quality of life and functional status, it is important to note that some contradictory results have emerged.[15,16] Furthermore, the determination of the minimal clinically important difference, especially concerning a modest decrease in cognitive test scores, remains uncertain. This has been a persistent issue in cognitive research for decades, particularly when evaluating the efficacy of anticholinergic and other dementia drugs. The widely recognized limited outcomes underscore the genuine impact of these drugs in dementia management, despite mere regulatory approval Figure 1.

Hippocampal Avoidance-Whole Brain Radiation Therapy (HA-WBRT) for Neurotoxicity Mitigation

Hippocampus-avoidance WBRT (HA-WBRT) selectively restricts the radiation dose in the hippocampal region with the intention of preserving cognitive functions. However, the clinical and neuroimaging evidence accumulated over the years reveals that RICT extends beyond hippocampal structures.[5,17] The notion that the preservation of hippocampal and surrounding medial temporal cortex (MTL) stem cells is crucial in encoding new information and learning, comes from the original article by Gondi et al.[18] This proposal also relies on the observation that radiation in the dentate gyrus reduces neurogenesis, resulting in a diminished population of granular cells. This decline could potentially impede their role in facilitating learning-dependent plasticity.[19] Nevertheless, the existence and extent of adult neurogenesis in the hippocampal dentate gyrus have become increasingly controversial.[20] Recently, single-cell RNA sequencing from 5 subregions of the entorhinal-hippocampal complex from human donors compared with other species, observed neural progenitors in other species but not in humans, suggesting the absence of significant neurogenesis as an endogenous process in adult humans.[21]

Memantine neuroprotection

Results

Phase 3 RTOG 0614 trial: primary endpoint (delayed verbal memory at 6 months) not statistically significant ($p = 0.0587$) but significant improvement in secondary endpoint, time to cognitive failure (TCF) at 6 months favoring memantine group (54% vs 65% placebo group).

Uncertainties

Significant loss of patients during follow-up

Executive functions yielded contradictory results

The minimal clinically important difference of a modest decrease in cognitive test scores remains uncertain

Hippocampal avoidance radiotherapy

Results

Phase 3 NRG CC001 trial: primary endpoint TCF showed a significant 26% reduction in cognitive decline in favor of HA-WBRT plus memantine (59.5% vs 68.3% WBRT plus memantine; HR 0.74).

Two Phase 3 trials comparing PCI vs HA-PCI: primary endpoint (verbal memory) resulted in contradictory results.

Phase 3 NRG CC003 trial: PCI-memantine vs HA-PCI-memantine: primary endpoint (delayed verbal memory at 6 months) not statistically significant. Secondary endpoint: TCF favor HA-PCI group plus memantine.

Uncertainties

HA relies on a hypothesis that is increasingly controversial and likely insufficient to mitigate the extensive brain damage associated with RICT

Significant loss of patients during the follow-up

Inconsistencies among trials and secondary endpoints

SRS instead of WBRT

Results

Phase 3 NCCTG N0574 trial: WBRT plus SRS vs SRS alone 1-3 BM: significant TCF at 3 months in favor of SRS alone (91.7% vs 63.5% for SRS alone).

Phase 3 NCCTG N107C trial: WBRT plus SRS vs SRS alone following BM resection improved cognitive rate at 6 months for SRS (52% for SRS vs 85% for WBRT)

Uncertainties

The suitable number and total volumes of lesions for SRS, balancing efficacy and safety is still not well defined

Figure 1. Controversies over prevention of radiation-induced cognitive toxicity (RICT).

Furthermore, cognitive impairment following cancer therapies can arise from other neurobiological mechanisms, such as disruptions in myelin homeostasis and plasticity. This mechanism involves adaptive changes in myelin structure, driven by neuronal activity, which modulates circuit function and optimizes cognitive function.[22] Moreover, microglia activation plays a significant role in regulating synaptic connectivity by removing synapses in an activity-dependent manner, thereby altering neural networks.[7,8,23] The intricate relationship between microglia and neurons allows them to collaborate in modifying white matter structure and functional connectivity, both of which are essential for efficient information processing. Recent research in the emerging field of cancer neuroscience[24] is reformulating our understanding of the complex interaction between neurons, glia cells, and cancer progression. This prompts consideration of how preserving the efficiency of existing neural networks and glia might affect the important crosstalk between the nervous and immune systems in brain cancer.

Additionally, recent research in neuroscience, emphasizing neural network dynamics,[25,26] has identified complex interactions between the medial temporal lobe, cortical and subcortical networks in memory and specifically in controlled retrieval of information. For example, recent evidence shows the clear involvement of the default

mode network in memory retrieval and autobiographical memory.[27–29] This shift, from focusing on simple and localized regions to considering the role of parallel neural networks sustaining complex cognitive processes, has led to the proposal of a theory of multiple-memory systems.

This theory is supported by complex network interactions involving, among others, the bilateral prefrontal cortex, the default mode network, parietal lobe (including the posterior cingulate cortex), subcortical regions, and the medial temporal lobe.[30–34] To preserve memory and learning as key outcomes for patients undergoing radiotherapy, it is essential to consider this emerging parallel memory systems framework, emphasizing the importance of preserving the structural and functional connectivity in these complex networks that participate in the storage and controlled retrieval of long-term knowledge. Preserving the hippocampal cortex is important for encoding new information. However, the impact of WBRT on other cortical regions and diffuse white matter, affecting structural connectivity, will probably impair the optimal performance of these networks. This could potentially affect memory and cognition, influencing the overall quality of life for patients.

Hippocampal Avoidance-Whole Brain Radiation Therapy (HA-WBRT) for the Treatment of Brain Metastases

Two small phase 2 trials, one randomized and the other contrasting with a historical cohort, compared HA-WBRT with conventional WBRT. These trials suggested that HA-WBRT might offer a slight advantage in preserving verbal memory function.[35,36] Subsequently, to confirm HA-WBRT and memantine efficacy, the NRG CC001 trial, a phase 3 randomized clinical trial, randomized 518 patients to receive either conventional WBRT or HA-WBRT, both in combination with memantine.[37] Interestingly, the number of patients randomized was higher than pre-specified in the sample size calculations. Moreover, the NRG CC001 trial faced challenges similar to the RTOG 0614 trial, with a significant loss of patients. The potential impact of brain metastasis progression was not considered when assessing cognition. Unlike the memantine RTOG 0614 trial and the previous phase 2 trials in HA-WBRT, the primary endpoint here was TCF, showing a significant 26% relative reduction in cognitive decline in favor of HA-WBRT plus memantine (59.5% vs 68.2% conventional WBRT plus memantine; HR 0.74).

Considering the heterogeneity in BM populations, patient dropout rates, variations in outcome assessment, and definition between the current HA-WBRT study (NRG CC001) and the RTOG 0614 trial, notable differences have emerged, particularly in the comparison of the TCF endpoint. Despite having similar BM populations in terms of age, performance status, and overall survival, these differences persist. Firstly, the TCF at 6 months for the WBRT plus memantine arms in the NRG CC001 and RTOG 0614 trials revealed noticeable differences (68% in NRG CC001 vs 54% in RTOG 0614), with the TCF for patients included in the NRG CC001 trial more closely resembling the placebo group (68% vs 65%) from the RTOG 0614 memantine trial. This suggests that patients with BM patients who underwent WBRT, with or without memantine, exhibited a comparable rate of cognitive impairment at 6 months. Additionally, there were inconsistencies in secondary endpoints, such as delayed recognition of verbal memory or executive functioning, and in terms of quality of life and patient-reported outcomes. Despite controversies over the study population definition, discussions about internal validity, effect size, and results interpretation, the findings establish the combination of HA-WBRT and memantine as the standard of care for patients with multiple BM who are not suitable for SRS Figure 1.

In light of these trials analyzed, a pivotal question emerges for designing cognitive neurotoxicity trials: What is the most suitable primary endpoint? Standardizing primary cognitive endpoints can enhance the comparability across studies and facilitate a more comprehensive evaluation of cognitive outcomes. For details, see Figure 2.

Another point to consider is that the feasibility of HA-WBRT is influenced by the distribution of BM and the margins used to define the HA region. Sparing the hippocampus can be challenging when metastases are nearby, although hippocampal involvement is relatively low (3%–8%),[38] increasing in patients with multiple BM.[38,39] Defining the HA region, typically with a 5 mm margin, requires advanced treatment planning techniques like intensity-modulated radiation therapy or volumetric modulated arc therapy to enhance feasibility.[35] Other patient-specific factors such as prognosis, baseline cognitive impairment, or lung cancer histology also yield different cognitive sparing benefits from HA-WBRT, as demonstrated in a secondary analysis of the NRG CC001 trial.[40] In summary, advanced planning techniques and careful consideration of patient-specific factors are essential for the feasibility of HA-WBRT.

Hippocampal Avoidance-Prophylactic Cranial Irradiation (HA-PCI) in Small-Cell Lung Cancer Population

To contribute further to this controversy, similar clinical trials have been conducted in patients with small-cell lung cancer (SCLC) who are undergoing prophylactic cranial irradiation (PCI). Two published randomized phase 3 trials comparing HA-PCI to standard PCI have shown conflicting results.[41,42] The first phase 3 trial ($n = 150$) showed a significantly lower rate of cognitive decline (verbal memory) at 3 months associated with HA-PCI (5.8% vs 23.5%) compared with PCI alone[42]; while the second trial ($n = 168$) found higher rates of cognitive failure (verbal memory) at 4 months in patients treated with HA-PCI, that were similar to those treated with PCI alone (29% vs 28%).[41]

In 2023, preliminary results of a phase 3 trial (NRG CC003) comparing HA-PCI plus memantine with PCI plus memantine ($n = 392$) showed no differences between groups in the primary endpoint of the 6-month verbal memory score.[43] However, HA-PCI plus memantine showed less cognitive failure, which was a secondary endpoint. In addition, a recent study reported a marginal decrease in hippocampal atrophy that did not correlate with differences in cognitive outcomes among patients who underwent HA-PCI compared with PCI. Both radiotherapy techniques were associated with declines in gray and white matter in other

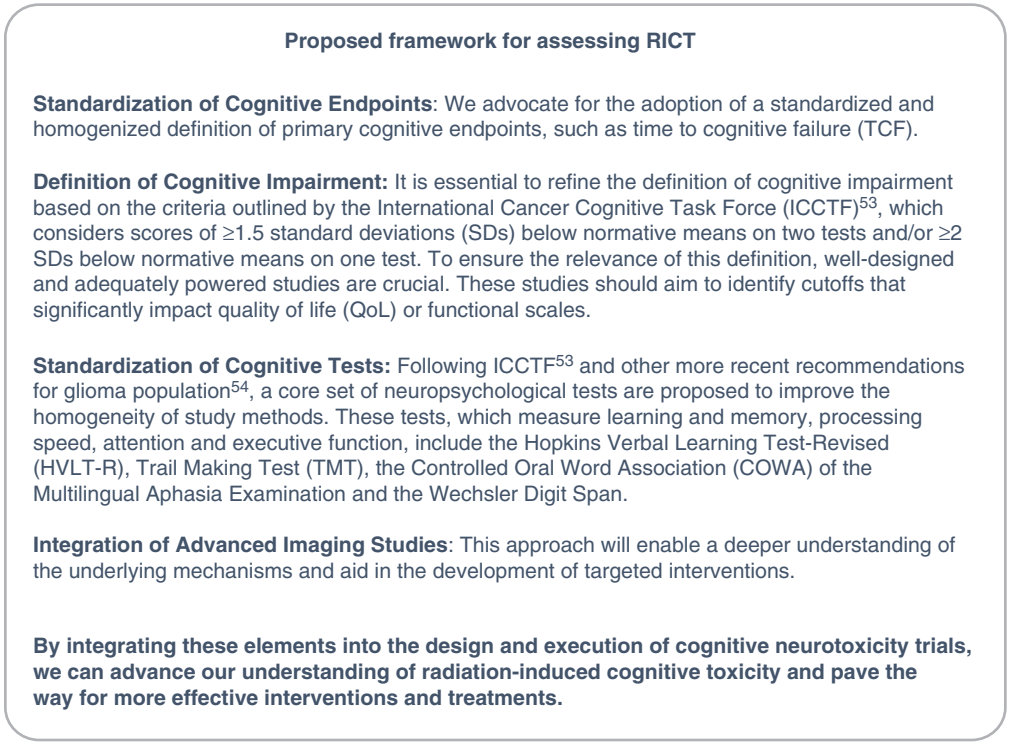

Figure 2. Proposed Framework for Assessing Radiation-Induced Cognitive Toxicity (RICT).

locations, irrespective of hippocampal sparing.[17] This suggests that incorporating advanced imaging techniques can provide valuable insights into the neurocognitive effects of radiation therapy on brain structure and function. See Figure 2.

On the other hand, a recent systematic review and meta-analysis comprising 109 studies on PCI, found that the PCI survival benefit is evident primarily in those SCLC patients with asymptomatic BM diagnosed through MRI. This suggests that the previously reported survival benefit may be attributed to the therapeutic rather than prophylactic effect of cranial irradiation. In light of this evolving understanding, prospective trials are needed that examine the effect of PCI on survival in patients with SCLC.[44] See Figure 1.

Cognitive Safety of Stereotactic Radiosurgery (SRS) for Multiple Brain Metastases

While WBRT has improved intracranial tumor control compared to SRS alone, it does not confer a survival benefit and is linked to increased cognitive decline and adverse effects on quality of life.[45] Early randomized trials (NCCTG N0574) evaluating the effect of adding WBRT to SRS versus SRS alone in patients with 1 to 3 BMs ($n = 213$) demonstrated substantial cognitive decline at 3 months (91.7% for WRBT plus SRS vs 63.5% for SRS alone) that persisted at 6 and 12 months.[46,47] In 2017, a phase 3 trial (NCCTG N107C; $n = 194$) demonstrated that adjuvant SRS, following brain metastasis resection, led to improved cognitive outcome (cognitive impairment rate at 6 months was 52% for SRS vs 85% for WBRT) with no compromise on survival but with lower intracranial brain control rates compared with WBRT.[48] See Figure 1.

However, SRS use carries an inherent risk of radionecrosis (4%–15%),[47–49] a condition that challenges clinical response assessment and often requires prolonged steroid use, which may led to discontinuation of immunotherapy. Despite these challenges, SRS emerged as an attractive treatment option, demonstrating efficacy with a more favorable cognitive profile than WBRT.

Although strong evidence supports SRS in managing limited numbers of BM, its use remains controversial in cases with larger numbers of BM lesions. A large multi-institutional prospective non-randomized longitudinal study included 1194 patients with 1 to 10 BMs (with a maximum total cumulative volume ≤15 mL) who were treated with SRS and showed non-inferior overall survival between patients with 2 to 4 compared to 5 to 10 metastases.[50] A subsequent secondary analysis, using Mini-Mental State Examination (MMSE), revealed 6%–9% of patients experiencing cognitive declines at 4 and 12 months, with no significant differences based on the number of BM.[51] However, MMSE while effective for established dementia, is largely insensitive for detecting moderate cognitive impairment.[52] This might explain differences in cognitive deterioration compared with seminal trials comparing SRS and WBRT.[46–48] This underscores the significance of homogenizing study methods, particularly in defining cognitive impairment and standardizing cognitive tests.[53,54]

For further insights into our proposed framework for assessing RICT, see Figure 2. Fortunately, ongoing trials, like NCT04277403 or NCT03550391, specifically focusing on assessing cognitive outcomes in patients with BM treated with SRS, will provide valuable insights into the optimal treatment strategy for patients with multiple BM.

Concluding Remarks

The core question regarding research efforts to improve the tolerance of WBRT needs to be reexamined. The QUARTZ phase 3 trial, particularly in patients with poor prognosis, showed that WBRT does not confer significant survival or quality-of-life advantages over best palliative treatment. However, controversies exist, particularly surrounding its potential utility in patients with favorable prognostic factors, as suggested by secondary analyses.

While refined WBRT techniques hold theoretical neurocognitive benefits, their impact on RICT appears marginal. HA-WBRT relies on a hypothesis that is increasingly controversial and likely insufficient to mitigate the extensive brain damage associated with RICT. Despite phase 3 trials favoring the use of HA-WBRT plus memantine, the lack of consistency in clinical outcomes across these trials creates uncertainty about the efficacy of these preventive measures in mitigating the overall cognitive impact of RICT. On the other hand, SRS emerges as the most radical local treatment for patients with multiple metastases, yet its cognitive risks, especially in long-term survivors benefiting from immunotherapy or targeted therapies, warrant consideration.

While no standard of care has yet been established for managing RICT, non-pharmacological interventions such are exercise, as well as promising pharmacological approaches targeting neuroinflammation, have emerged from several preclinical studies. Consequently, several pivotal clinical trials (phase I/II) are currently underway to evaluate their effectiveness, including exercise (NCT03169075), lithium (NCT01486459), renin–angiotensin system blockage ramipril (NCT03475186), and peroxisomal proliferator-activated receptors agonist pioglitazone (NCT01151670).[55]

It is also crucial to establish a consensus regarding the optimal primary neurocognitive endpoint for assessing RICT in the setting of BM. This standardization is essential for harmonizing trial designs and elucidating the real impact of cognitive variations on activities of daily living. TCF appears to be a reasonable endpoint for cognitive assessment in BM.

Future trials must carefully define the suitable number and total volumes of lesions for SRS, balancing efficacy and safety. Moreover, trials exploring new drugs with potential high penetrance on the central nervous system should be more inclusive allowing participation of patients with multiple BM without prior local treatments, particularly in patients with asymptomatic or olygosymptomatic BM. This design would enable a proper assessment of the new drugs and their impact on survival without excluding common clinical scenarios. This approach would assist in planning and sequencing treatments for patients with multiple BM sparing extensive irradiation for very exceptional clinical situations.

Keywords

brain metastases | cognitive toxicity | hippocampal avoidance | memantine | stereotactic radiosurgery

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Conflict of Interest Statement

Marta Simó has participated in lectures from Pfizer. Ernest Nadal has participated in advisory board or lectures from Roche, Bristol Myers Squibb, Merck Sharp Dohme, Merck-Serono, Sanofi, Pfizer, Lilly, Amgen, **Johnson and Johnson**, Daiichi-Sankyo, Boehringer-Ingelheim, AstraZeneca, Pierre Fabre, Qiagen, Takeda, Sanofi, Regeneron and **Genmab.** Ernest Nadal received research funding from Pfizer, Roche, BMS, and Merck-Serono and has participated as a consultant advisor for Apollomics, MSD, **Transgene** and Roche. Jordi Bruna has participated in advisory boards or lectures from Pfizer, Takeda, Boehringer-Ingelheim, and Novocure.

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