ScienceDirect

Cancer Letters

Volume 620, 28 June 2025, 217700

Pharmacological and therapeutic innovation to mitigate radiation-induced cognitive decline (RICD) in brain tumor patients

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Received 30 December 2024, Revised 1 April 2025, Accepted 4 April 2025, Available online 5 April 2025, Version of Record 9 April 2025.

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https://doi.org/10.1016/j.canlet.2025.217700

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Highlights

- Cognitive decline often occurs in brain tumor survivors post-radiotherapy.
- RICD is multifactorial, influenced by age, genetics, treatments& tumors.
- Neuroinflammation drives RICD in brain tumor survivors.
- Phytochemicals may treat neuroinflammation following radiotherapy.

- Early detection of RICD can be enhanced by advanced imaging techniques.

Abstract

Radiation therapy is a key treatment modality in both primary and metastatic brain tumors. However, despite its efficacy, it often results in cognitive decline, particularly after whole brain RT (WBRT). Radiation-induced cognitive impairment, which affects memory, attention, and executive function, significantly affects Quality Of Life (QOL) and functional independence. Although white matter necrosis, a hallmark of conventional radiation techniques, has become less common with modern methods, cognitive deficits remain a persistent issue. Neuroinflammation is a key driver of this decline, along with disruptions in hippocampal neurogenesis and damage to regions of the brain. Radiation affects neural stem cells, mature neurons, and glial cells, particularly within the hippocampus, affecting cognition. Recent studies suggest that targeting neuroinflammation and other key Signaling pathways (NMDAR, RAAS, PARP, PPAR, etc.) can reduce cognitive impairment. This review examines the theme of radiation-induced cognitive decline and explores possible interventions to prevent or mitigate these outcomes.

Introduction

Brain and central nervous system (CNS) tumors constitute some of the most lethal malignant neoplasms worldwide, with increasing incidence and mortality rates. Globally, there were approximately 3,50,000 cases of CNS cancers in 2019 [1]. In 2025, it is projected that there will be around 24,820 new cases in the United States alone, resulting in an estimated 18,000 deaths [2]. These tumors are particularly devastating in children, representing the most frequently diagnosed solid cancers and leading to the highest cancer-related mortality in this population [3,4]..

Current therapeutic strategies for brain tumors typically involve maximal safe surgical resection followed by adjuvant therapies, including radiation therapy (RT), which remains a mainstay, particularly for high-grade tumors. However, despite its efficacy in controlling tumor growth, RT is associated with significant neurotoxic effects, resulting in progressive cognitive decline. Radiation-induced cognitive impairment greatly impacts quality of life (QOL), which has become an increasingly important concern in improving survivorship. It is now recognized as one of the most critical components of brain tumor treatment outcomes, second only to survival in clinical trials [5,6]. As advancements in cancer treatments have improved survival rates, addressing the cognitive side effects associated with RT has become a priority.

This review examines cognitive dysfunctions in brain tumor patients, particularly radiation-induced cognitive decline (RICD), by exploring its molecular pathophysiology and evaluating potential pharmacological interventions, including drug repurposing and the use of

phytochemicals, to mitigate these effects. By identifying strategies to preserve cognitive function without compromising the efficacy of cancer treatment, this review aims to address a critical gap in the management of brain tumor patients.

Section snippets

Cognitive decline in brain tumor patients

Cognitive decline is a common late complication among brain tumor patients, particularly among long-term survivors and pediatric patients [[7], [8], [9]]. Cognitive deficits can significantly affect a patient's ability to manage self-care and engage in social and professional activities, influencing their overall quality of life (QOL, return to work, and reintegration into society. Among the extensively researched factors contributing to cognitive dysfunction are per *primum* tumor attributes …

Radiation-induced cognitive decline (RICD)

As previously discussed, RT is often associated with both acute and chronic toxicities due to a multitude of mechanisms that eventually culminate in cognitive decline, especially in pediatric patients. Nearly 90% of adult patients who survive more than six months after fractionated whole-brain radiation therapy (fWBRT) similarly experience cognitive impairments [46,38]. …

Strategies to mitigate radiation-induced cognitive decline

To address the challenges of radiation-induced cognitive decline (RICD), several strategies have been proposed, including modifications in radiotherapy techniques and the use of pharmacological interventions. Radiotherapy technique advancements, such as hippocampal-sparing approaches and stereotactic radiosurgery (SRS), aim to reduce radiation exposure to healthy brain regions, particularly the hippocampus, thus preserving cognitive function. Adjusting radiation doses and fractionation …

Early detection of radiation-induced cognitive decline

A critical research gap lies in the lack of validated biomarkers for early detection and risk assessment in RICD. Early diagnosis and monitoring of radiation-induced cognitive decline (RICD) are crucial for preventing long-term neurocognitive impairment and tailoring intervention strategies. The timely identification of changes in brain structure and function allows for the implementation of neuroprotective measures, thereby improving patients' quality of life.

Neuroimaging techniques such as …

CRediT authorship contribution statement

Jemema Agnes Tripena Raj: Writing – original draft, Visualization, Conceptualization. **Janmay Shah:** Writing – original draft, Visualization. **Shubham Ghanekar:** Writing – original draft, Visualization. **Geofrey John:** Writing – original draft, Visualization. **Jayant S. Goda:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Abhishek Chatterjee:** Writing – review & editing, Visualization, Supervision, Conceptualization. …

Funding source

None. …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Acknowledgement

All the images are created in BioRender. https://BioRender.com/e40q136 ↗ …

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This article is part of a special issue entitled: Cancer Neuroscience published in Cancer Letters.

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