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REVIEW

Radiation-Induced Cognitive Decline: Challenges and Solutions

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Abstract: Radiation therapy, a common treatment for central nervous system cancers, can negatively impact cognitive function, resulting in radiation-induced cognitive decline (RICD). RICD involves a decline in cognitive abilities such as memory and attention, likely due to damage to brain white matter, inflammation, and oxidative stress. The multifactorial nature of RICD poses challenges including different mechanisms of injury (neurogenesis, oxidative stress and neuroinflammation, dendritic structure alterations and vascular effects) and confounding factors like advanced age, and pre-existing conditions. Despite these challenges, several potential solutions exist. Neuroprotective agents like antioxidants can mitigate radiation damage, while cognitive rehabilitation techniques such as cognitive training and memory strategies improve cognitive function. Advanced imaging techniques like magnetic resonance imaging (MRI) help identify vulnerable brain areas, and proton therapy offers precise targeting of cancer cells, sparing healthy tissue. Multidisciplinary care teams are crucial for managing RICD's cognitive and psychological effects. Personalized medicine, using genetic and molecular data, can identify high-risk patients and tailor treatments accordingly. Emerging therapies, including stem cell therapy and regenerative medicine, offer hope for repairing or replacing damaged brain tissue. Addressing RICD is vital for cancer survivors, necessitating consideration of cognitive function and provision of appropriate support and resources for those experiencing cognitive decline.

Keywords: radiation therapy, radiation-induced cognitive decline, RICD, cognitive decline, cognitive function, central nervous system cancers

Introduction

Radiation therapy (RT) is a widely used cancer treatment modality for central nervous system malignancies that has been shown to have a detrimental effect on cognitive function. This decline in cognitive ability is known as radiation-induced cognitive decline (RICD).[1,2] Although a link between radiation treatments and cognitive decline has been established, the exact mechanism behind this damage remains properly understood.[3] While there are various potential causes, this review will focus on the most heavily researched and supported mechanisms. In addition to the difficulty in understanding the mechanism of RICD, diagnosing RICD in cancer patients is challenging due to lack of clarity regarding criteria and difficulty in accurately measuring cognitive function before and after radiation.[4]

RICD is considered a late effect of RT occurring in 30% or more of patients alive at 4 months after partial or whole brain irradiation. For those living over 6 months, that number may rise to 50%.[5,6] Maintaining cognitive function is important to brain tumor patients and a decline in cognitive function is generally accompanied by a decline in functional independence and performance status.[7] Here, we review the pathogenesis and management of RICD and discuss strategies used to minimize its risk.

Mechanisms of Injury

Neurogenesis

Neurogenesis is vital for brain development and function and persists in the lateral ventricles and hippocampus in adulthood.[8] Ionizing radiation reduces neurogenesis in the hippocampus's subgranular region and the lateral ventricles' subventricular zone.[9]

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The hippocampus, vital for emotions, spatial cognition, and memory processes, is especially susceptible to RICD due to its dependence on neurogenesis.[10,11] Radiation exposure has favored neural progenitors differentiating into astrocytic lineage, making damaged neurons irreplaceable.[5] These findings suggest that altering the neural environment significantly contributes to radiation's harmful effects on neurogenesis and related cognitive symptoms, and calls a need to explore possible solutions.

Oxidative Stress and Neuroinflammation

Radiation therapy induces oxidative stress which can harm the brain due to limited repair activity and high production of reactive oxygen species.[12] Studies have demonstrated that antioxidants like nigella sativa oil and thymoquinone can mitigate oxidative stress caused by radiation exposure to the head by reducing levels of lipid hydroperoxide, hydrogen peroxide, and total oxidant.[13]

The increase in free radical levels due to radiation therapy also results in the activation of tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β, which upregulates inflammatory pathways.[14,15] Brain inflammation presents with significant heterogeneity within the brain, with the hippocampus affected disproportionately, demonstrating inflammatory responses with activated microglia several months after exposure to radiation. The presence of microglia indicates increased production of both TNF-α and IL-6, which not only leads to pro-inflammatory responses within the hippocampus, but also contributes to neurogenesis inhibition.[14] When the brain is under normal conditions, only dendritic cells, T lymphocytes, and macrophages can enter through the blood brain barrier. However, after damage is done to the brain, microglia and astrocytes initiate an inflammatory response, causing an infiltration of lymphocytes and additional macrophages. These immune cells initiate a positive feedback loop as they release pro- and anti-inflammatory compounds, free radicals, and chemokines, which further propagate the release of inflammatory factors.

Inflammatory factors exhibit diverse impacts on neurogenesis. For instance, when initiating inflammatory responses, activated microglia produce an insulin-like growth factor 1 (IGF-1), which activates an extracellular signal-regulated kinase (ERK) and leads to increased neurogenesis within the subgranular zone (SGZ). Other inflammatory compounds that have been found to increase neurogenesis include a ciliary neurotrophic factor (CNTF), stromal cell-derived factor 1 (SDF-1), and more. On the other hand, there are inflammatory compounds that inhibit neurogenesis such as leptin and TNF- α.[16] Finally, there are inflammatory factors that have positive and detrimental effects. For instance, interferon gamma (IFN-γ) has been shown to promote the migration and differentiation of neural progenitor stem cells (NPCs), while also inhibiting the proliferation and promoting the survival of adult NPCs. Thus, radiation therapy triggers an inflammatory feedback loop in response to brain damage, with factors having both promoting and inhibitory effects on neurogenesis.[9,16] Further research is necessary to characterize the contradictory effects of such inflammatory factors on neurogenesis.

Dendritic Structure Alterations

Dendrites play a vital role in neural circuit function, and changes in their morphology can cause various neurological conditions. Specifically, dendritic spines are small protrusions that extend from dendrites in most excitatory synapses, and a change in the number of spines, either increase or decrease, can correspond to similar changes in the number of synapses and lead to circuit dysfunction.[17] This mechanism may explain the cognitive decline associated with radiation exposure and identifying therapies that can preserve dendritic structure and spine density could prevent such cognitive decline.

Duman et al explored radiation effects on mice, revealing extended reductions in dendritic projection density and an unexpected increase in excitatory synapse and dendritic spine density an hour after radiation.[18] The study found that these alterations led to abnormal glutamate activity and N-methyl-D-aspartate receptor (NMDAR) signaling. In other words, glutamate toxicity and abnormal NMDAR signaling were discovered to be a potential mechanism of RICD. The researchers then treated the mice with memantine, an NMDAR blocker, and found that the drug blocked a 2-fold increase in dendritic projection density induced by radiation exposure.

Alterations in dendritic structure can affect patient learning and memory, requiring a reliable risk prediction model. Low linear energy transfer (LET) radiation such as X-ray, gamma-ray, and high energy protons, has been implicated in

such damage. To understand the changes that LETs can have on mouse hippocampal dentate granule cell layer (GCL) and CA1 pyramidal neurons, a study utilized a model with two components that utilized energy deposition in dendritic segments (EDDS).[19] The first component determined whether a given branch of a dendrite would be damaged, and the second determined whether the damaged segments would eventually be repaired or cut out. The researchers found that radiation sensitivity typically decreased with the age of the neurons that were dividing. They concluded that rapidly dividing cells that are undergoing active metabolic processes are more sensitive. Incorporating age as a parameter in the future may provide better guidance for treatments, as there is currently no data showing the sensitivity of neurons at various stages and ages.

Another study sought to precisely identify the brain regions affected by inflammation in relation to dendritic cells. The study observed that microglia were responsible for increased dendritic damage. Microglia play a crucial role in the synapses between pre-synaptic and postsynaptic cells and are responsible for destroying synapses when connections are no longer required. In this study, researchers found that microglia were potentially removing the nodes that are at one end of a juncture, leading to those neurons being unable to make any connections in the future as well. Anterograde amnesia is one of the symptoms that patients may experience, and this study points out that microglia tend to target less mature spines, which are speculated to be important in encoding new memories. The research provides two possible approaches that can be preventative from neuronal damage: blocking the CR3 receptors that are implicated in the removal of synapses by microglia and tamping down the immune response during radiation. When the CR3 receptor was suppressed, the mice did not undergo any synaptic loss during radiation.[20]

Vascular Effects

Vascular effects of radiation therapy include endothelial cell death, thrombus formation, and vessel damage due to membrane thickening and collagen formation. These harmful radiation effects result in an accelerated development of both atherosclerosis and microangiopathy.[21,22] These changes in both vascularity and basement membrane thickening can be picked up by different screening techniques such as angiograms and can identify those at high risk of RICD. Identifying high risk patients of RICD in early stages allows for more immediate intervention and can lead to better patient outcomes.

Ischemia increases extracellular glutamate, an important excitatory neurotransmitter, potentially causing excitotoxicity in neurons through increased NMDA receptor activation. Targeting this pathway through various mechanisms, such as p38 and sterol regulatory element-binding protein 1, can help improve excitability levels in the brain, which can improve patient outcomes and prevent cerebral injury due to radiation exposure.[23]

A vascular hypothesis details radiation-induced vascular changes, including vessel dilation, vasculopathy, endothelial progenitor depletion, and apoptosis. These changes occur in acute and later phases, affecting capillaries, basement membranes, and endothelial activity. Radiation-induced damage to capillary endothelium can also have deleterious effects on the blood-brain barrier leading to devastating health outcomes.

Mitigation Strategies

Stem Cell Therapy for Neurogenesis Damage

Stem cell therapy offers a potential solution to counteract radiation-induced neurogenesis damage.[24] Recent research exposed animals to radiation and transplanted stem cell-derived oligodendrocyte progenitors into their corpus callosum to assess cognitive improvements. It was found that in animals with the transplantation, an improvement in tasks testing memory and learning capacity was observed. When examined further, these animals demonstrated axon remyelination and a restored population of glial cells.[25] Similarly, transplanting human pluripotent stem cell-derived cells into rats' post-radiation promotes neuron regeneration and reduces hippocampal inflammation, improving RICD conditions.[26] A distribution of stem cells along the hippocampal septotemporal axis and reduced microglial activation was found. The distribution along the septotemporal axis favored a neuronal fate, and the reduced activation of microglia indicated downregulation of inflammatory pathways. Proper regeneration of neurons and lowered inflammation in the hippocampus promotes proper conditions for improvements to be made to RICD (Figure 1).

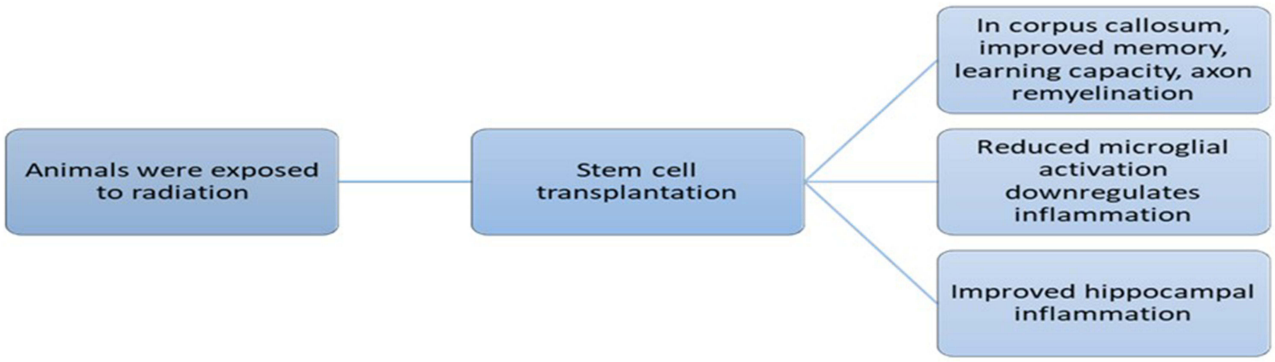

Figure 1 Stem cell therapy for neurogenesis damage.

In summary, modifying the neural environment may be crucial in radiation's impact on neurogenesis and cognitive decline. Stem cell therapy could be a viable solution to address the detrimental effects of radiation on neurogenesis and may provide a promising avenue for treatment.

Anti-Inflammatory Agents for Oxidative Stress and Neuroinflammation

Anti-inflammatory agents can improve radiation-induced cognitive injury by mediating the neuroinflammation feedback loop (Figure 2). Previous studies have found that rats exposed to radiation therapy and treated with indomethacin, an anti-inflammatory agent, for two months had a 35% reduced activation of microglia. In addition, they found less recruitment of peripheral monocytes, which indicates normalization of endothelial cell inflammation.[27,28] Monje et al then discussed how the reductions in neuroinflammation associated with nonsteroidal anti-inflammatory drugs (NSAIDS) affects cognitive function and highlighted that both memory and the capacity to learn can be better preserved after irradiation with anti-inflammatory agents.[27]

Memantine for Dendritic Structure Alterations

Presently, memantine is the standard for preventing RICD, serving as a noncompetitive NMDA receptor antagonist that inhibits glutamate binding under pathological conditions. The reductions in glutamate binding prevent extended calcium release, which is the mechanism by which excitotoxicity is induced (Figure 3).

Brown et al showed that memantine was well tolerated and had a toxicity profile very similar to placebo. Overall, patients treated with memantine had better cognitive function over time; specifically, memantine delayed time to

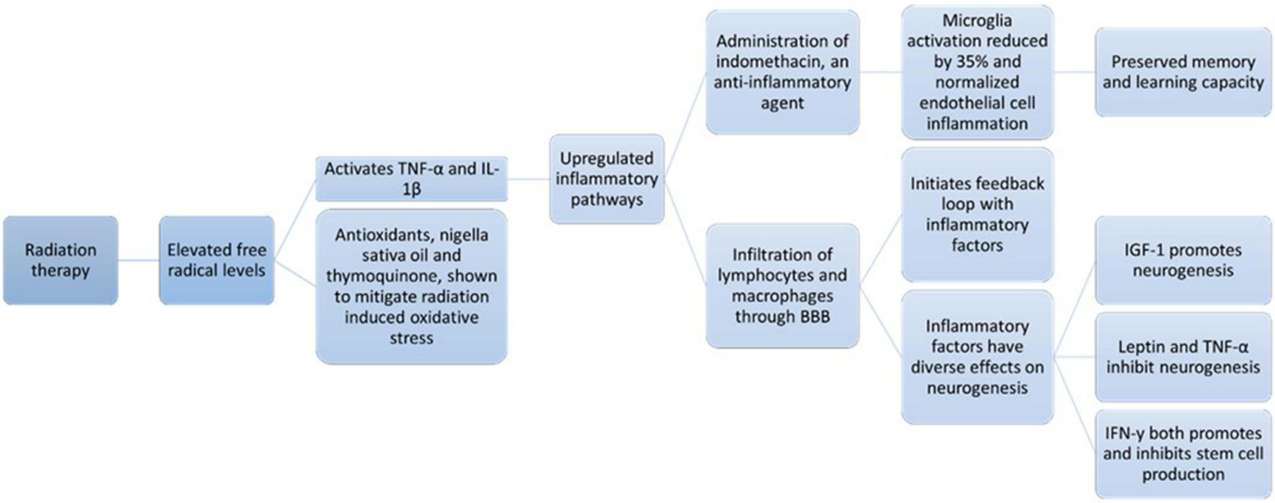

Figure 2 Anti-inflammatory agents for oxidative stress and neuroinflammation.

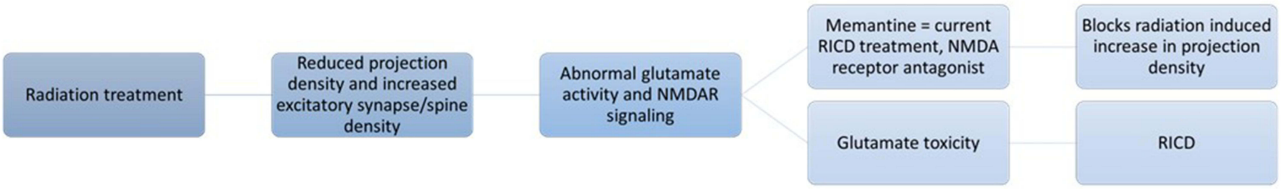

Figure 3 Memantine for dendritic structure alterations.

cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBRT.[29]

Other pharmacologic treatment options include donepezil, methylphenidate. Donepezil is an acetyl-cholinesterase inhibitor indicated for mild to moderate Alzheimer's Dementia. Rapp et al showed that patients randomized to donepezil performed better on measures of verbal and working memory (HVLT-DR and - IR) as well as a measure of motor speed and dexterity (Grooved Pegboard).[30]

Methylphenidate is a stimulant approved for treatment of Attention-Deficit Hyperactivity Disorder (ADHD) and ADD. Mulhern et al showed that methylphenidate can improve fatigue, attention, and cognition in children who received WBRT and in patients with chemotherapy-related fatigue.[31] But Butler et al by presenting a randomized, open-label, placebo-controlled Phase III trial of methylphenidate taken during brain RT and for 8 weeks after showed no difference in FACIT-F scores or cognitive measures.[32]

Cyclooxygenase-2 (COX-2) Inhibitors, Erythropoietin (EPO) for Vascular Effects

While radiation-induced brain injury mechanisms remain unclear, Cyclooxygenase-2 (COX-2) inhibitors like Celecoxib can preserve the blood-brain barrier integrity in rats, reducing brain injury.[33]

Along with this, Celecoxib was also shown to have protective effects on the human brain microvascular endothelial cells against radiation by inhibiting apoptosis and decreasing the ratio of products such as thromboxane B2 and 6 keto Prostaglandin F1α (PGF1α).[34]

The hippocampus plays a major role in memory and adult neurogenesis and preserving it during radiation prevents cognitive deficits and decline. Various therapies can protect against vascular damage by reducing apoptosis and inhibiting inflammation with use of erythropoietin (EPO), renin-angiotensin system (RAS) blockers, stem cells, and enriching environments.

EPO is a neuroprotective agent that is used in many disorders, including Alzheimer's disease, Parkinson's disease, and demyelinating diseases. In rodent studies, EPO administration protects against motor impairments and memory deficits from radiation. However, recently, EPO has not been validated due to its adverse effects on tumor control.[35] Rather, most novel strategies have focused on anti-inflammatory drugs such as peroxisome proliferator-activated receptor alpha (PPAR- α) agonists (fenofibrate) and transplantation of neural stem cells[36] (Figure 4).

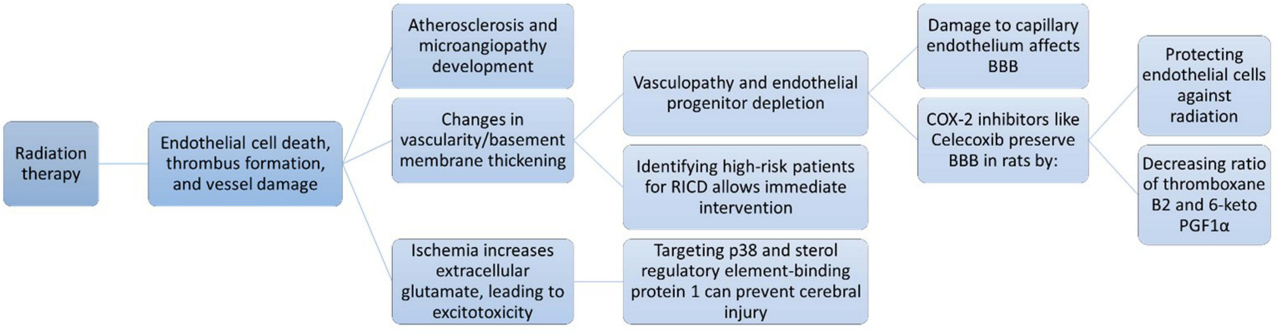

Figure 4 Cyclooxygenase-2 (COX-2) inhibitors, erythropoietin (EPO) for vascular effects.

Cognitive Training/Memory Strategies

While there are medications and treatments available to alleviate the symptoms of RICD, cognitive interventions can be effective in retaining cognitive function. Kesler et al investigated a cognitive training program's impact on cognitive function in breast cancer survivors, leading to notable enhancements in executive function, verbal fluency, memory, processing speed, and cognitive flexibility. It's important to mention that these patients underwent chemotherapy treatment instead of radiation. Additionally, the study had a limited sample size.[37]

In another study, Sciancalepore et al reviewed the effects of computer-based cognitive interventions on pediatric patients diagnosed with brain tumors and treated with chemo-radiation therapy.[38] The study found that cognitive intervention led to significant improvements in working memory and attention. However, like the previous study, there were limitations in the sample size and patient adherence to the intervention. Hence, future research is needed with larger sample sizes and greater patient involvement to improve the acceptance of cognitive intervention treatments.

While cognitive interventions can be helpful in mitigating the effects of RICD, patients can also use memory strategies to reduce cognitive deficits. Memory strategies improve memory with techniques like repetition and visualization, enhancing cognitive function in both healthy and impaired individuals.[39]

Furthermore, cognitive interventions and memory strategies offer potential to reduce RICD. Further research is needed, but these techniques have shown promise in preserving cognitive function in cancer survivors.

Proton Therapy

Proton therapy is an alternative to radiation therapy due to its precision and tissue-sparing capability. Shih et al showed low toxicities of proton therapy in 20 low-grade glioma patients over five years. It found no association between proton treatment and cognitive decline in the first five years. These findings suggest potential benefits of proton therapy in reducing RICD. Note that the study had a small sample size and proton therapy is costly compared to traditional photon-based radiation therapy.[40]

Brown et al showed that hippocampal avoidance (HA) using intensity-modulated radiotherapy during whole-brain radiotherapy (WBRT) plus memantine better preserves cognitive function and patient-reported symptoms, with no difference in intracranial progression-free survival (PFS) and overall survival (OS), and should be considered a standard of care for patients with good performance status who plan to receive WBRT for brain metastases with no metastases in the HA region.[41]

Takaoka et al compared hippocampus sparing after whole brain radiotherapy (WBRT) to intensity-modulated proton therapy (IMPT). IMPT reduced hippocampus D mean by 37% and D100% by 59%, showing proton therapy's potential to minimize cognitive decline from hippocampus damage.[42] Overall, proton therapy shows promise as an alternative to radiation therapy for preventing RICD.

Gondi et al prospectively investigated a potential predictive relationship between neurocognitive impairment and hippocampal dosimetric parameters. Hippocampi receiving less than 7.3 Gray (Gy) to 40% volume demonstrated statistically significant cognitive benefit.[43]

Although studies have demonstrated relatively low toxicities associated with proton therapy, more research is needed with larger sample sizes to confirm the effectiveness of this treatment option. Furthermore, the high cost and limited availability of proton therapy compared to radiation therapy may limit its accessibility for some patients.

Role of Patient-Related, Disease-Related and Treatment Related Factors on RICD

In understanding RICD, it is essential to consider the distinct influences of patient-related, disease-related, and treatment-related factors. Patient-related factors such as the age at irradiation and baseline cognitive status significantly affect the susceptibility and extent of cognitive decline, with older age and pre-existing cognitive deficits often leading to worse outcomes.[44]

Disease-related factors, including the tumor's location, overall disease burden, and the presence of hydrocephalus, also play critical roles, as tumors in or near critical brain regions and extensive disease can exacerbate cognitive impairments.[45]

Treatment-related factors, comprising surgical interventions, chemotherapy, co-medications, and specifics of radiation therapy such as dose, volume, technique, modality, and fractionation, are pivotal in determining the risk and severity of RICD. Each factor's contribution must be examined individually to develop comprehensive strategies for mitigating cognitive decline in patients undergoing radiation therapy.

Identifying High-Risk Patients for RICD

Improving cognitive decline after radiation therapy through medication and interventions is important in reducing RICD. However, another critical factor is identifying high-risk patients through biomarkers and neurocognitive tests.

As we know, the most common finding in RICD is white matter hyperintensities near the lateral ventricles (leukoencephalopathy and cerebral atrophy or cerebral microbleeds). Chapman et al evaluated cerebral white matter degradation in 10 patients subjected to fractionated brain radiation therapy using diffusion tensor imaging. The patients underwent an MRI before, during, and after the therapy to assess changes in both longitudinal and perpendicular diffusivity. In addition, the patients were asked to take a neurocognitive test and quality of life survey. The study showed early declines in parahippocampal cingulum diffusivity as an RICD biomarker, correlated with reduced verbal recall scores after radiation.[46]

Magnetic resonance spectroscopy (MRS) can detect early RICD. The study analyzed MRS metabolites in the corpus callosum before and after radiation therapy on 10 low-grade glioma patients. Neurocognitive tests (ACE-R and MoCA) also assessed decline. Findings showed significant corpus callosum N-acetylaspartate (NAA)/creatine (Cr) and choline (Cho)/creatine (Cr) ratio decreases during radiation and lower cognitive scores at 4 weeks of radiation therapy and 1–6 months post-radiation, suggesting MRS metabolites can identify high-risk RICD patients.[47]

Decreases in N-acetylaspartate (NAA), a biomarker indicative of neuronal damage, can aid in RICD detection.[48] Additionally, Cho, a marker for membrane turnover and integrity of white matter, was also examined.[49] Cr, an energy metabolism compound, is used as an internal reference in MRS because it has a rather stable peak throughout both health and disease.[50] Li et al analyzed [NAA]/[Cr], [Cho]/[Cr], and [NAA] and [Cho], and found higher CVs for [NAA]/[Cr] and [Cho]/[Cr] compared to [NAA] and [Cho].[51] Hence, the findings support using NAA and Cho metabolites to screen for high-risk RICD patients, but reducing Cr's variability is crucial before using MRS metabolites.

Overall, these studies suggest that identifying high-risk patients for RICD is crucial in improving cognitive decline after radiation therapy. Future research should focus on developing reliable biomarkers and neurocognitive tests to identify high-risk patients and developing interventions to prevent RICD.

Conclusion

This literature provides several plausible mechanisms to explain the cognitive decline observed in patients undergoing radiation therapy. Neurogenesis, the process by which stem cells differentiate into new neurons, is an essential process that maintains the integrity of certain brain structures, such as the hippocampus and lateral ventricles.[8] Radiation has been shown to direct stem cells to follow an astrocytic lineage rather than their role as neurons or glia, which reduces neurogenesis. This reduction in the ability to regenerate neurons can lead to RICD, leaving structures reliant on neurogenesis in a weakened state.[9–11]

Oxidative stress is another mechanism discussed in the literature as playing a role in RICD.[12] The production of free radicals can lead to upregulation of inflammatory pathways in the brain, which can have a multitude of effects on brain structures such as reduced neurogenesis and reduced nutrient supply.[14,15] Leaving neurons in such a vulnerable state can result in reduced cognitive function.

Dendritic structure alterations are a third mechanism discussed in this literature for playing a role in RICD. Changing either the structure or density of dendritic spines can lead to changes in signal transmission, which can affect cognitive function.[17] Additionally, radiation has been shown to increase excitatory dendritic spine density, leading to increased glutamate toxicity.[19]

Finally, radiation therapy can lead to the occlusion of blood vessels due to thrombus formation, which can lead to endothelial cell death. In addition, ischemia is associated with glutamate toxicity in the brain, which can result in a reduced cognitive function. The mechanisms discussed in this literature highlight the detrimental effects of radiation

therapy, but also demonstrate methods by which we can reduce the extent of cognitive decline in patients receiving therapy.[21,22]

Stem cell therapy and immunotherapy are potential areas to explore to preserve neurogenesis and cognitive function.[52] Anti-inflammatory agents have been shown to counteract oxidative stress and downregulate inflammatory pathways, indicating their potential role in aiding RICD.[27,28] Memantine, a treatment that reduces glutamate binding and prevents excitotoxicity, is currently considered the standard of care for patients treated with whole brain radiation to prevent RICD.[53] Due to its beneficial role in addressing RICD, treatments that target dendritic structure alterations and glutamate toxicity need to be further explored.

Proton therapy is a rarer, but also expensive treatment, but studies have shown that its precision and sparing of surrounding tissue can prevent the cognitive decline in patients who undergo radiation therapy.[40,42] Finally, cognitive training has shown promise in improving cognitive decline in cancer survivors treated with chemotherapy, and future research is needed to determine if similar improvements can be observed in cancer survivors treated with radiation therapy.[37]

Disclosure

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