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Brain irradiation and long-term cognitive disability: Current concepts

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Abstract

Standard treatment of primary and metastatic brain tumors includes high dose megavoltage radiation to the cranial vault. About half of patients survive >6 months, many attain long term control or cure, but 50-90% of survivors overall exhibit disabling cognitive dysfunction. The radiation cognitive syndrome is poorly understood and there is no effective prevention or long-term treatment. Attention has primarily focused on mechanisms of disability appearing at six months to one year after radiotherapy. However, a range of studies have revealed that CNS alterations and dysfunction develop much earlier than 6 months following radiation exposure. This has prompted the recent hypothesis that relatively subtle early forms of radiation induced CNS damage may drive chronic pathophysiology leading to permanent cognitive decline. Within this perspective, the present review presents evidence of acute CNS irradiation triggered inflammation, and injury to neuronal lineages, accessory cells and their progenitors, and loss of supporting structure integrity. Moreover, injury related processes set in motion soon after intracranial irradiation may interact and synergize to alter the neuronal and supporting cell progenitor signaling environment in stem cell niches in the brain, and specifically in the hippocampus, a structure critical to memory and cognition. Changed niche conditions may cause a sustained decline in neurons and progressive deterioration of cognition. The concluding discussion addresses, **(1)** what further data is needed, and **(2)** potential treatment interventions, identified via recent findings on acute CNS radiation injury, that may reverse degenerative processes before they can cause permanent cognitive disability.

I. Introduction

Every year many hundreds of thousands of patients worldwide undergo radiotherapy for primary brain tumors and for brain metastases originating from extracranial tumors.[1-5] Radiation is an indispensable treatment mainstay for the majority of these brain tumors.[6-9]

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Brain radiotherapy is subdivided into whole brain radiotherapy (WBRT) in which the entire brain and brainstem are irradiated, and partial brain radiotherapy (PBRT) which includes treatment of the tumor or tumor bed and surrounding margin, and some healthy brain tissue subject to incidental irradiation [4,10,11] Stereotactic radiosurgery (SRS) relies on precise 3D imaging and localization to deliver ablative doses of radiation to the tumor, and can significantly reduce exposure of healthy brain tissue.[12] These modes of brain radiotherapy fulfill any of a range of clinical objectives including; (1) long term tumor control or cure as mono or combined therapy, (2) salvage treatment for slowing tumor growth or palliation, and (3) prophylaxis to kill metastatic cells that would otherwise become established in the brain.[6,13-15]

Presently about 100,000 brain tumor patients per year in the U.S. receiving brain irradiation survive >6 months, and 50-90% of these individuals exhibit cognitive dysfunction which is often progressive and disabling.[3,16-18] Affected cognitive domains include learning, memory, processing speed, attention, and executive function.[8,19] Patient quality of life (QOL) is now accorded great importance in clinical oncology, and radiotherapy-induced cognitive decline erodes patients' perception of QOL as revealed by a questionnaire from the cognitive section of the European Organization for Research and Treatment of Cancer (EORTC).[20-2218,22] The World Health Organization (who) describes health as a “state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity” (http://www.who.int/about/definition/en/print.html). The Response Assessment in Neuro-Oncology (RANO) working group recommended that neurocognitive outcome be considered as one of the primary endpoints in brain tumor clinical trials.[23] Despite the importance and clear concern about radiation induced cognitive decline, the pathophysiology driving the progression of this syndrome remains poorly understood, and there are no effective preventative measures or long-term treatments.[24]

The genesis of radiation induced cognitive decline is complex with multiple interacting and synergistic mechanisms.[25-27] Historically, the primary focus has been on markers of damage and cognitive decline appearing over 6 months to 1 year or more after irradiation.[5] For example, white matter deterioration has been presumed to be a major factor underlying progressive cognitive decline that is generally apparent a year or so after brain irradiation.[18] Questions inevitably arose because of reports describing the absence of demonstrable white matter changes despite the presence of cognitive impairment.[18,28,29] More sensitive imaging modalities such as diffusion tensor imaging (DTI) along with new lines of inquiry and enhanced experimental techniques in animal and cell based systems have been able to reveal subtle evidence of damage to white matter, the cortex, and a range of neuroanatomical domains at various levels of resolution much sooner than 6 months.[5,18] In many studies CNS changes were observed within hours, days, or weeks of irradiation. For the present review the term early refers to acute events developing at 4 weeks (1 month) or less after radiation exposure.[27,30,31]

We and others postulate that previously undetected and comparatively subtle early manifestations of irradiation damage to the central nervous system (CNS) may synergize over time to form long-term macro and microstructural abnormalities, resulting in permanent cognitive disability.[5,18,25] Early changes below the gross anatomical level, including a

decline in oligodendrocytes, microvascular damage, subtle loss of white matter integrity imaged with DTI, neuroinflammation, and disturbances of neuronal micromorphophysiology, may interact and progressively alter neuronal stem cell niches to impede neuronal function, viability, and progenitor cell differentiation.[5,18,30] This scenario may result in long-term dysfunction and depletion of neurons and contribute to cognitive decline.[4,5,32,33]

This review begins by delineating the rationale for CNS radiotherapy and identifying the impacted cognitive domains. This is followed by a description of the time course of cognitive deterioration, and the evidence acquired from preclinical models supporting the concept that early radiation induced subtle changes in the brain are precursors to long-term, permanent CNS dysfunction (Figure 1). Evidence gathered via the longitudinal imaging of brain injury in human radiotherapy patients is then addressed in the context of **(1)** early and long-term CNS deterioration and cognitive disability, and **(2)** major hypotheses of radiation induced cognitive decline. The concluding discussion transitions to future directions and to potentially relevant opportunities for early therapeutic interventions, based on early CNS damage that may be exploited to impede progressive cognitive deterioration.[3-5,18,30,33,34]

II. Intracranial Radiotherapy--- Effective but with Serious Risks to Cognition

The initial barrier to success in treating brain tumors is resistance and local treatment failure allowing tumor recurrence and expansion.[35,36] Multiple biological processes contribute to treatment failure in both primary and metastatic brain tumors, but it is generally held that the key obstacle is the inability of drugs to attain effective intra-tumoral concentrations.[36,37] In contrast radiation uniformly penetrates both the brain and tumor parenchyma, engages macroscopic and microscopic disease, overcomes resistant cells, and thus is an essential therapeutic modality.[6,8]

For example in adult medulloblastoma patient cohorts with nondisseminated disease, craniospinal irradiation and chemotherapy have achieved a 5 year survival of 70%.[38]

Despite its undisputed therapeutic importance radiation often unavoidably damages the brain and affects cognition.[27] The neurocognitive domains thought to be most affected by radiation are verbal and non-verbal memory, executive function, sustained attention, and information processing speed.[8,39] The hippocampus is instrumental in learning and memory, while the prefrontal cortex (PFC) plays a key role in executive functioning and data shows it is affected by radiation.[27,40-42] The underlying brain networks involved in sustained attention and processing speed are thought to be more distributed in nature, with most evidence suggesting that they rely on a complex frontal-subcortical network that involves both cortical and white matter structures.[43,44] Radiation injury may affect some or all of these pathways, is multifactorial and complex, and is characterized by vascular abnormalities, inflammation, gliosis, demyelination, and often at high doses, white matter necrosis.[3,45]

III. The Time Course of Neurocognitive Dysfunctionin Radiotherapy Patients

Wu and colleagues have noted that attention has largely focused on potential mechanisms of cognitive deterioration appearing at six months to one year following brain irradiation, rather than early abnormalities and how they may evolve over time.[5,46] The cognitive decline developing after 6 months is held to be progressive and irreversible and is thus of the greatest concern (Figure 2).[18,6,27] In the adult patient population, which is the focus of the present review, radiation induced neurocognitive decline follows a biphasic pattern beginning with a transient cognitive decline at approximately 4 months posttreatment, followed by an improvement, and then a progressive, irreversible deterioration in cognitive functioning at 12 months or later after irradiation.[6] However, it is important to note that tumor progression during this time period may adversely affect cognition, confounding imaging and the measurement of radiation-induced cognitive decline in many studies. Radiation necrosis occurs in a minority of patients and its probability is low at doses below 50 Gy given in 2 Gy fractions.[6,47] However, the incidence increases substantially with escalating radiation dose, fraction size, and the use of chemotherapy.[47,48] The most frequent neurotoxic effect of cranial irradiation at any patient age is not focal necrosis but diffuse cerebral injury.[49] Importantly, radiation-induced cognitive decline occurs at doses much lower than those that can cause radionecrosis.[50]

IV. Early Radiation Induced CNS Abnormalities in Preclinical Animal Models

Perhaps somewhat surprisingly, early CNS functional changes developing in animal models after irradiation were noted decades ago. Gangloff reported that altered hippocampal spike activity persisting for 7 days appeared in the cat and rabbit following 4 Gy of X-rays.[51] Bassant and Court found immediate alterations in the firing patterns of rabbit hippocampal neurons with 4 Gy of gamma radiation.[52] Pellmar and Lepinski found evidence that 5 Gy to the Guinea pig resulted in a decrease of synaptic efficacy soon after irradiation, with apparent recovery by 5 days.[53] These results suggest that the hippocampus expresses radiation induced damage early, and an important conceptual question that has not been addressed until quite recently is whether early changes are somehow related to later dysfunction, progressive deterioration, and permanent cognitive deficits.

Early Radiation Injury to Brain Blood Vessels

Early vascular disruption in preclinical models such as the rabbit ear, evidenced by edema developing within hours of a single radiation dose, followed by vascular dysfunction months later, was first reported in the 1950s.[54,55] Since then a considerable body of accumulated evidence has shown that radiation early destabilizes the plasma membrane of a range of cell types including the vascular endothelium.[3,56] Cranial irradiation has reduced endothelial cell density in rat brains within a day of 5-200 Gy, and this dose-independent loss persisted for one month after exposure, followed by a slow dose-independent decrease in cell number for 6 months, and thereafter the cell population remained depleted.[31] Microvascular sequelae of endothelial degeneration seen in humans may occur months to years after the initial radiation induced damage, and include telangiectasias, microvascular dilatation, and thickening and hyalinization of the vessel wall.[57] Such changes can trigger ischemic strokes,

brain microbleeds, and occlusion of small vessels, leading to local necrosis and extravasation with subsequent demyelinization.[58] Intracerebral cavernous malformations which are susceptible to bleeding have been observed in human patients with a median latency of 3 to 6 years following CNS irradiation.[45,59,60] Disturbances of cerebral blood flow have been associated with cognitive debility, and the extent of hypoperfusion has correlated with the depth of cognitive deterioration.[61,62] Vascular damage and associated sequelae leading to poor perfusion of brain tissue can secondarily cause local demyelination and focal necrosis which degrade cognition.[47] Vascular endothelial and glial cell loss has been presumed to cause white matter damage and subsequent cognitive impairment.[63] White matter networks play an essential role in supporting cortical function and cognitive dysfunction has been linked to damage within these networks (Figures 3 & 4).[27,64] However, radiation induced vasculopathy alone may not entirely account for the progressive cognitive decline that occurs after WBRT. Greene-Schloesser et al note that in the rat, drugs such as the PPARγ agonist, pioglitazone, and the ACE inhibitor Ramipril do not effect improvement in the microvasculature after it has been damaged and depleted after irradiation, but both agents have been reported to prevent radiation induced cognitive decline.[18,65,66]

Astrocytes – Early Radiation Effects

Glial cells comprise a major proportion of the cellular population of the brain, they control a range of essential functions, and have long been implicated as a causative factor in radiation induced cognitive decline.[67] How glial cells are affected by radiation and how they contribute to radiation induced cognitive decline remains unclear. Astrocytes are glial cells that have a major role in the mature CNS, supporting neurons, maintaining homeostasis, and modulating neurotransmitter dynamics.[68] Following intracranial irradiation astrocytes proliferate and form scar tissue, referred to as reactive gliosis.[69] Hwang et al reported that a single dose of 15 Gy radiation to the rat brain increased immunostaining of GFAP in astrocytes at 6 hours with increased staining at 24 hours, which the authors interpreted as the onset of gliosis.[70,71] Identifying features of reactive gliosis are hypertrophy of astrocytic processes, upregulation of intermediate filaments, and increased glial fibrillary acidic protein (GFAP) expression.[70,72] Their experiments suggested that PGE_2 released from irradiated microglia is a trigger of radiation-induced gliosis.[70] How astrocytic activation and dysfunction may affect white matter, may be affected by neuroinflammation, and in general contribute to cognitive decline requires further investigation. It has been reported that irradiation of microglia-astrocyte co-cultures and astrocyte monocultures results in the expression of inflammatory cytokines.[73] Some evidence indicates that treatment with Ang 1-7 peptide may prevent radiation-induced MAP kinase activation and inflammation, which could in theory reduce radiation-induced cognitive impairment.[73]

Oligodendrocytes – Early Radiation Effects

Oligodendrocytes are glial cells thought to be the most radiation sensitive cell type in the CNS, they produce and maintain myelin sheaths along neuronal axons. Early developing global reductions in their numbers has been observed in rodent brains within a few hours of intracranial irradiation.[74,75] The majority of cycling cells in the adult brain (>75%) are oligodendroglial precursors and loss of these cells is presumed to diminish the replacement of oligodendrocytes.[76] Following cranial radiation in animals manifestations of white matter

injury such as focal demyelinization and necrosis have been observed.[77] Panagiotakis et al using rats head irradiated with 25 Gy of 250 Kv X-rays observed a reduction in oligodendroglial lineage cells and ultrastructural evidence of myelin fragmentation, but did not find evidence of vascular damage.[76]

The Role of Cranial Radiation Dosing Regimenin Glial Loss and White Matter Damage

Comparatively recent reports suggest that the nature of the brain irradiation dosing scheme appears to significantly influence specific pathologies in the human and animal brain (see Table 1).[9,28,78] In rats following a high single intracranial dose (25 Gy) of 250 kV X-rays, Panagiotakis et al assessed oligodendrocyte lineage cell populations over 15 months.[76] Markers for mature (MBP) and developing (NG2, O4, PDGFRA) oligodendrocytes revealed that cell numbers at all differentiation stages showed an initial early drop followed by a variable pattern for several months, and finally an apparently permanent decline at about 12 to15 months after irradiation.[76] Moreover, at the 15 month time point a diffuse pattern of myelin loss was observed throughout the corpus callosum as well as the fimbriae, the external capsule and the deep white matter.[76] In contrast, fractionated intracranial irradiation was investigated by Shi et al and delivered as 9 exposures to 5 Gy over 4.5 weeks for a total of 45 Gy in middle aged (12 month) Fischer 344× Brown Norway rats, a regimen that closely emulated human radiotherapy treatment schedules.[29] At 12 months post-irradiation white matter gross morphology and structural integrity were normal (Table 1).[29] Importantly, despite normal appearing CNS anatomy in the Shi et al study, a fractionated 45 Gy intracranial radiation dose in this F344 rat model has caused hippocampal and non-hippocampal dependent cognitive deficits, along with glutamate receptor abnormalities.[79] These results align with other studies in preclinical models and with human subjects which have both uncovered moderate cognitive deficits in the absence of evident structural changes on neuroimaging.[57] Chen et al exposed rat pup subventricular zone progenitor cells *in vitro* to 8 Gy of γ-rays and concluded that neither the percentage of stem cells nor their proliferation was affected, although progression through the cell cycle was markedly delayed, and, interestingly, the proliferation of a glial-restricted precursor was increased.[80]

Early Post-Irradiation Neuroinflammation, Vascular Damage, and the Hippocampus

Adult neurogenesis mainly occurs in two brain regions, **(1)** the hippocampal dentate gyrus and subgranular zone (SGZ) and **(2)** the subventricular zone (SVZ).[81,82] Radiation is now known to suppress the proliferation of hippocampal SGZ progenitor cells and their differentiation into neurons.[83-86] Murine hippocampal cells undergo reduced neurogenesis after 5 Gy or 10 Gy of intracranial X-irradiation, and the mice exhibit reduced cognitive abilities in maze tests.[87,88] Radiation induced hippocampal impairment is currently thought to derive from damage to differentiated neural cells, altered neurogenesis,[89] and a resultant loss of hippocampal plasticity.[83,84,90] In line with this theory, Acharya et al. reported that human neural stem cell transplantation attenuated radiation-induced cognitive dysfunction in head irradiated mice.[91,92] The hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex are particularly sensitive to vascular injury, and radiation has been hypothesized to cause vascular rarefaction in the hippocampus and cognitive dysfunction that is reversible with hypoxia.[62,93]

Astrocytes and microglia respond to brain irradiation by secreting factors that induce widespread neuroinflammation that can impact cell function and differentiation in the CNS.[25,94] Proinflammatory cytokines such as interleukin-1β, tumor necrosis factor-α, interleukin-6 and interleukin-18 have been measured in specific regions of the brain following radiation exposure.[95] Inflammatory markers such as GFAP, intercellular adhesion molecule-1 and NF-κb have also been identified in irradiated brain tissue.[96] COX-2 pathways have been implicated in neuroinflammation following intracranial irradiation and the expression of prostaglandin E2 has been suggested as a cause of radiation gliosis.[70,97] Monje et al examined neuropathological markers of neurogenesis and inflammation in the human hippocampus after intracranial radiation treatment for early myelogenous leukemia and MB and found evidence of inflammation with virtually complete inhibition of neurogenesis.[98] Inflammation in the hippocampal microenvironment causes microvascular damage which also results in the release of signaling molecules, thereby changing the progenitor cell microenvironment which suppresses differentiation to the neuronal phenoptype.[94,98-101] A trophic relationship exists between microvessels and neural progenitors, and the levels of VEGF in the hippocampus have been shown to affect hippocampal angiogenesis and neurogenesis, and to modulate hippocampal plasticity of mature neurons.[102,103] The above findings suggest potential therapeutic strategies such as the use of anti-inflammatory agents and implantation of neural stem cells.[98,94] Jenrow et al reported that pharmacologically based reduction of neuroinflammation during a 9 month period following a single intracranial 10 Gy dose of gamma radiation to adult male Fisher F344 rats resulted in a higher proportion of hippocampal progenitors adopting a neural instead of a glial fate compared to untreated controls.[10] The authors suggested that this outcome was due to an improved neurogenic signaling microenvironment. Importantly, the comparatively long time span of this study points to the possibility that neuroinflammation may be chronic after irradiation, and exerts protracted effects on the neuronal population, glial cells, and white matter, thus driving progressive cognitive deterioration.[10,27]

V. Early Radiation Damage to the Neuronal Lineage and Progressive Cognitive Dysfunction

Classically the brain has been regarded as a radio resistant organ, and neurons as essentially inert to radiation.[5,18,104] However, some writers drawing on both old and new observations posit that differentiated neurons are not inert to radiation as previously thought, and suggest that neuronal dysfunction and not neuronal loss is the driver of radiation induced cognitive debility.[5,90] In accordance with this view, Lee and colleagues found reduced hippocampal neurogenesis following irradiation of young adult male rats despite pharmacologic blockade of Angiotensin II mediated inflammation, yet, importantly, these animals did not exhibit radiation induced cognitive impairment.[66] Perhaps this was because the neuronal precursor population is small compared to the mature neuronal compartment and hence its disruption may be insufficient to cause identifiable hippocampal cognitive deficits.[34]

Shi and coworkers demonstrated cognitive impairment in rats after fractionated WBRT, yet quantitative analysis of hippocampal neuron number and myelin integrity in the same model indicated neither hippocampal neuron loss nor changes in myelin integrity.[2,17,29,79] Why this

study differs from other reports is not clear, possibilities include the rodent model and radiation dosing scheme. Another possibility is that microanatomical and functional deficits at the neuronal level occur soon after irradiation, without an immediate loss of neuronal density, apparent white matter damage, or detectable loss of gray matter volume.

Early Neuronal Microanatomical Abnormalities After Irradiation

Robbins et al (2011) performed a head radiation study using healthy adult male rhesus monkeys, without chemotherapy or surgery.[105] These authors reported that 40 Gy in 5 Gy fractions were associated with impaired Delayed-Match-to-Sample (DMS) cognitive performance and reduced prefrontal cortical glucose uptake.[105] The temporal pattern of cognitive decline in the monkeys over the course of 11 months closely mirrored the apparent cognitive course of human intracranial radiotherapy patients.[105] In the context of the present review, a key question is whether the cognitive decline observed for rhesus monkeys was preceded by early CNS damage. Possible microanatomical correlates of early radiation induced neuronal dysfunction include changes in neuronal dendritic spine density and morphology. Dendritic spines are sites of synaptic contact and their morphophysiology is thought to provide the basis of specific components of cognition such as long-term potentiation (LTP) and plasticity.[106-108]

Dendritic spines are actin-rich protrusions of neuronal dendrites and are the site of excitatory synaptic transmission.[109] They are highly dynamic structures populated by NMDA-type glutamate receptors which are activated by strong synaptic input. [109] Activation triggers calcium flux into the spines and cytoskeletal rearrangement that generates larger spines with stronger synapses. Such changes in synaptic strength are held to comprise the primary basis of learning and memory.[109] Frankfurt and Luine related histology and behavioral tests in rats and identified a clear relationship between dendritic spine density in the hippocampus and memory.[107] In the PFC early stress in humans and animals and mental illness in human patients can cause atrophy of dendrites and spines, and this is associated with working memory impairment.[110] Dendritic spines in the pyramidal neurons of the PFC and the hippocampus, brain structures which orchestrate executive function and memory, respectively, change with aging and this correlates with behavioral decline.[111] Brizee reported changes in dendritic morphology following prenatal irradiation of squirrel monkeys with 2 Gy of X-rays.[112] Parihar and Limoli and Parihar found changes in dendritic morphology and plasticity in hippocampal slices from mice following doses of 0.1 and 1 Gy of protons or 1 and 10 Gy of X-rays at early time points, 10 and 30 days post-irradiation.[30,34] Significant reductions in the number of dendritic branches, branch points, and dendritic length were observed at 30 days indicating a reduction in dendritic complexity.[30,34]

Early Alterations in the Neuronal Signaling and the Hippocampal Progenitor Cell Microenvironment After Intracranial Irradiation

The hippocampus depends on the differentiation of thousands of neurons each day to subserve cognition and memory.[113] These neurons are generated from progenitors in the subgranular zone of the dentate gyrus (DG) which secrete VEGF.[114,115] Immature neurons are mainly post-mitotic and migrate into the DG granule cell layer (GCL) where they differentiate into mature neurons.[116] Mature glutamatergic neurons in the GCL of the DG

form spines in the molecular layer of the hippocampus where they receive input from the entorhinal cortex (EC).[116] Ambient GABA (γ-aminobutyric acid) is instrumental to the proper maturation of neurons[117] This process of neurogenesis is supported by an exquisite niche comprised of glial cells, neurons, astrocytes which secrete Wnt, oligodendrocytes, extracellular matrix and remodeling microvasculature.[32,114,118] Damage to any component of this niche may be expected to dysregulate neurogenesis. Implantation of neuronal precursors has been found to mitigate radiation induced cognitive decline, although Monje and colleagues (2002) found that transplants of non-irradiated neural precursor cells did not differentiate into neurons in the irradiated hippocampus.[89,91,119] The authors suggested the failure to differentiate was caused by, **(1)** an altered microenvironment due to disruption of the microvascular angiogenesis associated with adult neurogenesis, and **(2)** a marked increase in the number of activated microglia causing inflammation within the neurogenic zone.[89,93] In a recent study however, Bostrom reported that a high single dose of 8 Gy to the brain of young male C57BL/6 mice caused over one year, progressive depletion of neurogenesis without disruption of the neurovascular niche.[120]

Several authors have speculated that early dysfunction of surviving neuronal cells alters the signaling microenvironment thus influencing progenitor cell differentiation and cognitive capacity over the long-term.[5,121,122] For example Wu et al reported that the *ex vivo* irradiated rat hippocampal dentate gyrus exhibited early decreases in tyrosine phosphorylation and loss of excitatory N-methyl-D-aspartate receptors (NMDARs) from the cell surface.[5] At the same time the surface expression of gamma-aminobutyric acid receptors (GABARs) was increased.[5] Moore and coworkers (2015) observed subtle changes related to both hippocampal and cortical signaling (2014), discovering that the Homer1a receptor binding protein in young adult male Fischer 344 × Brown Norway rats at 48 h after 40 Gy of fractionated WBRT was elevated in the hippocampus and decreased in the cortex.[4] Homer1a engages only family 1 metabotropic glutamate receptors (mGluR) and inhibits their binding to the synapse.[123] At 2 months following irradiation homer1a expression was reduced in both the cortex and hippocampus, and correlated with downregulation of hippocampal glutamate receptor 1 and protein kinase C_{γ}, and cortical up-regulation of glutamate receptor 1 and protein kinase C_{γ}.[4] Overexpression of Homer1a in the hippocampus is known to abolish maintenance of CA3-CA1 long-term potentiation (LTP), synaptic plasticity and to impair working memory.[124-126] These are functional hippocampal effects that are duplicated by radiation exposure.[46,127] Over the long term, months to years, dysregulated signaling may cause hippocampal precursor cells to differentiate into glia rather than neurons, resulting in a loss of neurons and the plasticity required for learning, memory, and other aspects of cognition.[102,128-130] Importantly, other radiation induced effects such as inflammation may interact with signaling changes within the neurogenic SGZ niche to worsen dysregulation of progenitor cells in the hippocampus and elsewhere in the brain.

VI. Neuroimaging Evidence for Radiation Induced CNS Changes in the Context of Time Course and Prevalent Biological Hypotheses of Potential Mechanisms

Structural Changes in White and Gray Matter Brain Territories

Presently imaging is the only way by which to chronicle CNS damage in a radiotherapy patient over time. White matter plays a key role in linking cortical territories in cognition while gray matter (cortex) especially in the frontal, temporal and hippocampal regions plays a vital role in memory and cognition. Detection and interpretation of white matter damage is challenging with standard MR imaging approaches. The extent of detectable white matter damage may depend on age (Table 1, Figure 5).[18,77,105,113] One study of glioblastoma patients found that standard chemoradiation led to progressive volume loss of the non-tumor bearing brain hemisphere, with DTI changes in the subventricular (progenitor cell) zone.[131] Karunamuni et al used cortical volumetry of high resolution MRI and showed dose-dependent cortical atrophy in high grade glioma patients one year after PBRT (Figure 6).[132] This study also showed a greater degree of dose-dependent cortical atrophy in the limbic and temporal lobes. These authors went on to study the selective vulnerability of cerebral cortex, showing that regions critical for higher-order cognition (entorhinal cortex and inferior parietal cortex) are the most sensitive to radiation-related atrophy.[133] The same authors in another study modeled radiation-induced cortical atrophy, showing feasibility of sparing eloquent cortex with advanced planning techniques.[134]

Imaging Changes in the Hippocampus

Neuroimaging evidence of radiation-induced hippocampal changes are mixed. A study in head and neck cancer patients with low-dose incidental RT to the hippocampus found no volume changes, and the study cited above in glioblastoma patients found no hippocampal volume changes 6 months after start of chemoradiation.[131,135] However one recent study found progressive hippocampal volume loss after chemo-radiation in malignant glioma patients.[136] Seibert and colleagues analyzed hippocampal volume changes after PBRT in patients with primary brain tumors, and found significant radiation dose-dependent atrophy with a 6% volume loss in high-dose regions after one year, Figure 7.[137] Studies correlating imaging biomarkers with neurocognitive effects in brain tumor patients are underway. A pilot functional imaging study using FDG PET showed that decreases in CNS metabolism after radiotherapy correlated with neurocognitive decline for problem solving and cognitive flexibility.[61] No early changes seem have been reported in neuroimaging studies, but changes in neuronal structure and function may occur early along with vascular damage and inflammation, eventually leading to volume changes that are detectable on imaging.

Early Neuronal Abnormalities Detected by MR Spectroscopy

Neuronal damage in patients may be signaled early after irradiation by changes in brain chemical constituents.[138] N-acetylaspartate (NAA) is a neuronal marker, and Walecki et al reported a decline in the Cr/NAA ratio in brain tumor patients one month after WBRT with 60 Gy given in fractions of 1.8-2 Gy.[138] The authors attributed this effect to neuronal dysfunction rather than neuronal loss.[138] Sundgren et al also found early NAA decreases

that persisted, being evident at 3 weeks, 1 month and 6 months after 50.4-59.4 Gy of fractionated PBRT.[139] These radiotherapy patients had low grade glioma (LGG)or benign brain tumors, and, importantly, NAA changes developed in brain regions that appeared normal on MRI imaging.[139] Movsas et al in a small study examined NAA levels in lung cancer patients receiving either palliative or prophylactic fractionated 30-37.5 Gy WBRT, and found a statistically valid decrease in NAA, with no significant difference between prophylactic and palliative groups.[140] The timeframes generally described by these studies align with the timeframe for radiation induced changes in neuronal architecture reported by Parihar et al.[30,34]

Early White Matter Changes After Irradiation Revealed by Diffusion Imaging (DI)

Novel, high resolution imaging techniques can be used to study radiation-induced brain injury with precision and high spatial resolution. Diffusion-weighted imaging (DWI) is more a sensitive MR based technique by which microstructural changes in white matter integrity may be detectable[141,142]. DWI measures and models the diffusion of water at the cellular level[143] and diffusion-tensor imaging (DTI) models the motion of water as an ellipse, with derived metrics allowing the study of white matter integrity.[144] Several studies have used DTI to study the effects of radiation on normal appearing brain white matter, specifically as biomarkers of demyelination and axonal dysfunction shown in preclinical models.[27,131,142,145,146] While one study suggested that DTI was only sensitive to radiation changes above a threshold dose of 45-50 Gy,[147] others have shown changes in DTI metrics with doses as low as 5-15 Gy and dose dependent DTI changes.[27,146,148] Importantly, Connor et al found CNS white matter changes on DTI appearing as early as one month after irradiation of glioma patients.[27]

Diffusion Imaging and Synergism Between Different Forms of CNS Radiation Damage

Connor and colleagues utilized advanced diffusion imaging with different diffusion weightings, showing dose and time dependent white matter changes which favor a primarily extra-axonal component of white matter injury.[27] This suggests early changes in the white matter microenvironment like neuroinflammation may contribute to white matter/axonal injury. Another recent study found that diffusion changes in individual white matter bundles were associated with maximum dose to those tracts, implying serial radiation injury.[149] There also appears to be regional susceptibility of white matter damage. A study of medulloblastoma survivors found greater diffusion changes in the frontal versus parietal lobes.[150] Another study found prominent diffusion changes in the fornix and cingula after WBRT.[151] Several DTI studies have correlated white matter diffusion metrics with neurocognitive changes, for example Chapman and colleagues found that diffusion changes in the parahippocampal cingulum were associated with late decline in verbal recall after radiotherapy.[152] Khong correlated changes in diffusion parameters after WBRT in childhood cancer survivors with intelligence quotient scores.[153]

VII. Conclusions

Given the fact that the CNS contains many structures potentially sensitive to radiation, it is probable that the irreversible cognitive deterioration that so often follows intracranial

radiotherapy is multifactorial in its origins.[27] The present review posits the concept that early brain tissue abnormalities, which have in fact recently been identified, may lead to chronic interactive pathologies that progress to permanent cognitive deterioration. For example early inflammation affects the hippocampal microenvironment and may exacerbate dysregulated neurogenesis because of neuronal damage and altered signaling in the progenitor cell microenvironment. Widespread inflammation may affect white matter integrity and oligodendrocyte progenitors elsewhere in the brain.[154] In addition white matter comprises part of progenitor cell niches in the brain and thus may adversely affect progenitors and repair mechanisms.[155] A key need at the present juncture is a framework of how differential brain compartment susceptibilities are distributed across patient populations and in distinct preclinical models. This needs to be accompanied by an experimentally validated definition of the nature and extent of early CNS damage according to specific radiation dose ranges and fractionation schedules, and how such early damage evolves and synergizes over the long term to create permanent cognitive disability.[26]

The lack of an overview and mechanistic understanding of radiation induced cognitive decline has forced clinical investigators to base the selection of candidate therapeutics on extrapolations from other CNS disorders, with the unsurprising result that patient responses have been mixed and short term in nature. Methylphenidate, which in the past has yielded some beneficial results, and memantine, which is in clinical testing, are both well tolerated and may be helpful in select radiotherapy patients.[156,157-159] A current clinical trial (NRG CC-001) is examining memantine and WBRT with and without hippocampal sparing. Acetylcholinesterase inhibitors, e.g., donepezil, are being pursued as they have produced some positive results in Alzheimers and other dementias.[18,160,161] On the other hand anti-VEGF agents in brain tumor patients have elicited serious concerns since in clinical testing the small molecule VEGF-A inhibitor bevacizumab appears to have worsened cognitive decline by possibly further inhibiting hippocampal plasticity.[162]

New strategies may evolve from recent demonstrations that neuronal architecture may be damaged by radiation. Protein Kinase C (PKC) over expression reduces neuronal dendritic spine density in the hippocampus and PFC.[163,164] Hence PKC inhibitors such as chelerythrine, and staurosporine analogs such as midostaurin which has been approved for use in patients, may help protect against deleterious changes in dendritic architecture.[164,165] Benzothiazole amphiphiles promote the formation of dendritic spines in primary hippocampal neurons and may help overcome the effects of radiation.[166] In addition recent data suggests that stem and progenitor cells are likely key targets in radiation brain injury and cognitive decline, stem cell niches may be compromised by inflammation, vascular damage, and extracellular matrix destruction. Stem cell niches are distributed throughout the brain, so one approach may be to ‘re-engineer’ CNS stem cell niches soon after irradiation.[167] Aggressive and early use of anti-inflammatory agents may prove beneficial, along with direct injection or targeted administration of nanoparticles bearing biomimetic extracellular scaffolds which have shown benefits in animal models of inflammatory CNS injury, gels, bioactive signaling molecules for stem and microvessel endothelial cells, and stem or progenitor cells.[168] Moreover, small molecules such as fluoxetine, which is a selective serotonin reuptake inhibitor, have promoted the maturation of neurons and enhanced neurogenesis in animal models.[169]

Future studies may offer translational promise by focusing on newly emerging data showing early post-irradiation changes that have the potential to impact neuronal support elements and the signaling environment in neuronal progenitor cell niches within the brain. In this regard progress may be expected based on, **(1)** the careful consideration of radiation dosing regimens, **(2)** more sensitive brain imaging methods for longitudinal biomarker[18] and anatomically oriented studies, especially in the context of CNS changes developing before 6 months after irradiation, and not all patients may be equally vulnerable **(3)** subtle morphologic and functional changes on the neuronal level,[18] **(4)** the role of inflammation, and **(5)** the long-term signaling microenvironment in terms of neuronal progenitor cell differentiation. In aggregate these elements may facilitate a deeper appreciation of evolving radiation induced brain abnormalities at multiple levels. This would certainly establish a more concrete foundation for rationally based studies aimed towards the identification of early preventative measures and therapies to impede degenerative processes before cognitive decline can become permanent.

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Biographies

Milan Makale, PhD, Assistant Professor, Radiation Medicine and Applied Sciences, UC San Diego Moores Cancer Center, Dr. Milan Makale is an assistant professor at the UC San Diego Moores Cancer Center. Dr. Makale's background is in radiation biology and bioengineering, and his research interests are focused on improving the efficacy and tolerability of radiation therapy for cancer. Dr. Makale is developing tumor selective small molecule and nanoparticle based radiation sensitizers for solid tumor therapy. He is also pursuing improved understanding and characterization of normal tissue injury that is associated with radiotherapy, and is exploring nanoparticle and stem cell niche engineering based approaches to promote tissue recovery.

Carrie McDonald, PhD, ABPP-CN, Associate Professor of Psychiatry, Center for Multimodal Imaging and Genetics (CMIG) University of California, San Diego, Dr. Carrie McDonald is an Associate Professor of Psychiatry at UC San Diego and a board-certified neuropsychologist with expertise in the presurgical evaluation of patients with epilepsy and primary brain tumors. Her research focuses on multimodal imaging of patients with epilepsy for predicting cognitive and seizures outcomes following neurosurgical interventions, as well as understanding the effects of radiation therapy on cognitive decline in patients with brain tumors. She directs the Brain Tumor Neuropsychological Assessment Clinic at UC San Diego and is an active member of the Center for Multimodal Imaging and Genetics.

Jona Hattangadi-Gluth, MD, Assistant Professor of Radiation Medicine and Applied Sciences, Associate Director, Imaging Research, Center for Translational Radiation Medicine and Imaging, Dr. Jona Hattangadi-Gluth is a board-certified radiation oncologist and Chief of the Central Nervous System Tumor Service in Radiation Medicine at UC San Diego. She is a national expert in the treatment of patients with brain tumors, serving on the National Comprehensive Cancer Network panel for the treatment of brain tumors. Her research focuses on the use of advanced MRI techniques in radiation planning and measuring response to radiation in brain tissue. She is the principal investigator on several investigator-initiated clinical trials including a longitudinal study of advanced diffusion imaging and serial neurocognitive testing to measure radiation-induced injury in brain tumor patients.

Santosh Kesari, MD, PhD, Chair, Department of Translational Neuro-oncology and Neurotherapeutics, John Wayne, Cancer Institute. Director of Neuro-oncology, Providence Saint John’s Health Center, Dr. Santosh Kesari is a board-certified neurologist and neuro-oncologist and is currently Chair, Department of Translational Neuro-oncology and Neurotherapeutics, John Wayne Cancer Institute. He is also Director of Neuro-oncology,

Providence Saint John's Health Center and Member, Los Angeles Biomedical Research Institute. Dr. Kesari's research focuses on improving our understanding of the molecular and biological basis of brain tumors. A physician/scientist, Kesari leverages his background in normal tissue and tumor biology, and radiation therapy to, **(1)** better understand the natural history of brain tumors and identify potential therapeutics, and **(2)** develop strategies for addressing the recovery of normal tissues after chemoradiotherapy.

Key Points

- Intracranial radiotherapy leads to permanent and significant cognitive disability in 50-90% of patients.
- The pathophysiology remains poorly understood and there are no effective preventative measures or long-term treatments.
- Historically, the primary focus has been on markers of damage and cognitive decline appearing 6 months to 1 year or more after irradiation.
- More sensitive imaging and new lines of inquiry have revealed subtle evidence of central nervous system (CNS) damage much sooner than 6 months after radiation.
- These early forms of CNS damage may persist and synergize over time to form long-term and irreversible deficits in neuronal and supporting cell lineages vital to cognition.
- Consideration of early forms of radiation induced CNS damage may help identify early treatments to reverse degenerative processes before they can cause permanent disability

Review Criteria

The database searched was primarily PUBMED together with extensive google inquiries based on search terms including; cognitive decline/deterioration and radiation, intra/cranial radiation/ radiotherapy, progenitor cells, glioma, medulloblastoma, radiotherapy brain tumors, radiation vascular, glial cells and radiation, hippocampus physiology and anatomy, hippocampus and radiation, inflammation and radiation, neurons and radiation, among others too numerous to list. Primarily peer reviewed research papers and recent reviews were examined. Publications listed in review articles were acquired and considered, and frequently their bibliographies were also pursued. Publications older than 1990 were generally not included, the majority of papers are 2-3 years old, and the emphasis was on publications less than 10 years old. However, some older papers showing early radiation effects in the brain and vasculature were included, as these had been ignored for many years, but are now important landmarks and relevant to recent thinking that acute effects do occur and that these may evolve and conspire to cause permanent cognitive disability after radiotherapy.

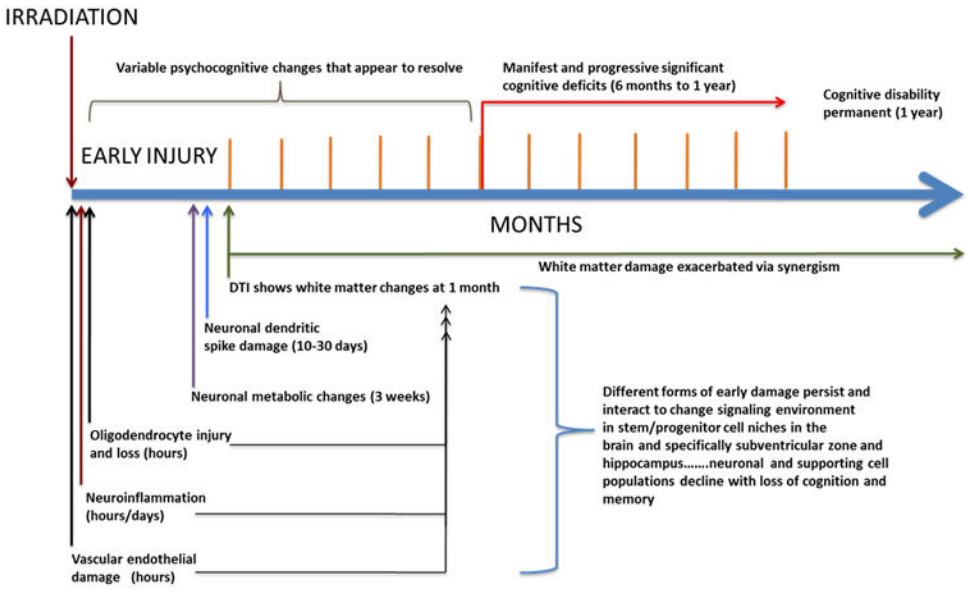

Figure 1. Evidence for early radiation injury to the CNS

A proposed time course and scheme by which early damage becomes chronic and the interactions leading to permanent cognitive disability.

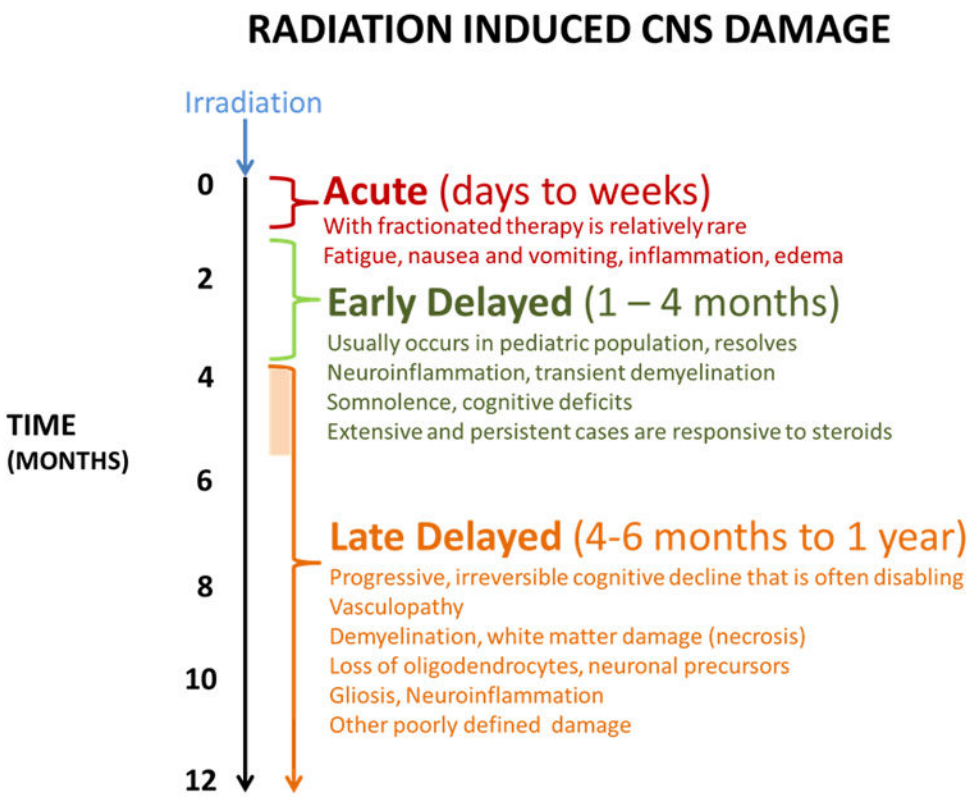

Figure 2.
Manifestations and time course of radiation induced CNS injury and cognitive decline.

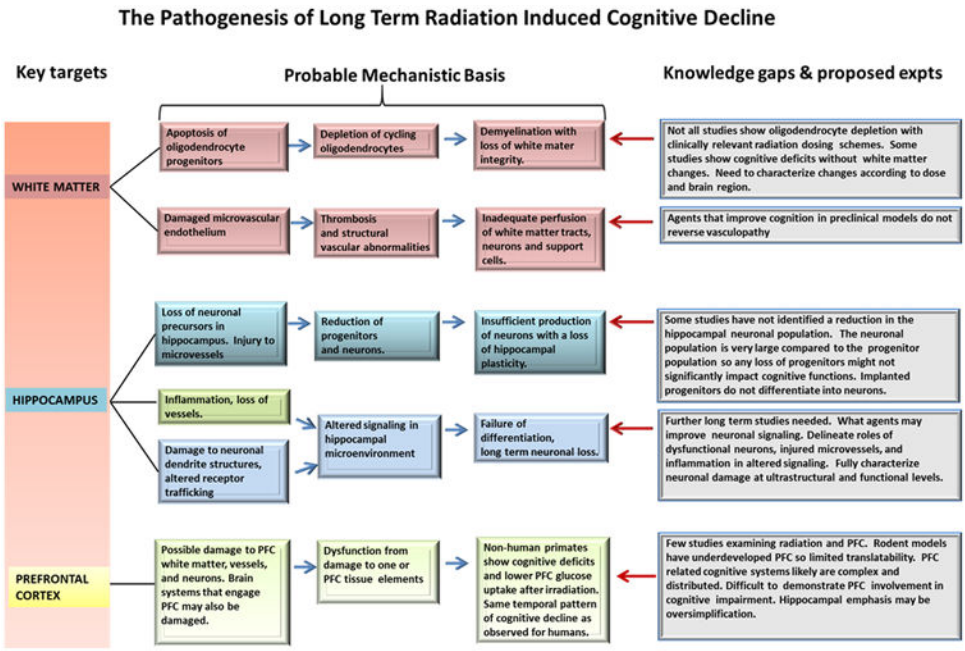

Figure 3. Primary radiation induced CNS abnormalities

Detailed scheme shows major proposed mechanisms contributing to radiation induced cognitive decline.

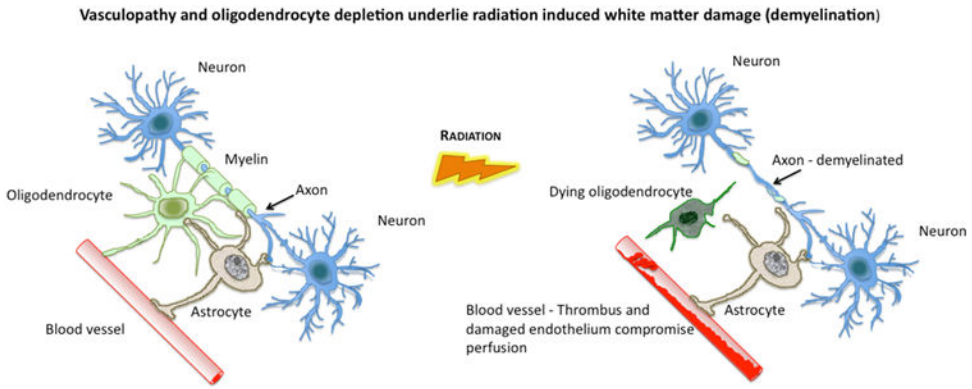

Figure 4. The presumed origins of white matter damage

White matter provides essential connectivity for cortical function. Oligodendrocytes establish and maintain myelin around white matter axons (left panel) and their destruction (right panel) results in a loss of myelin integrity. Damage to feeding microvessels (right panel) also compromises white matter but also has adverse effects on the perfusion of other key CNS elements such as astrocytes which provide metabolic and functional support to neurons.

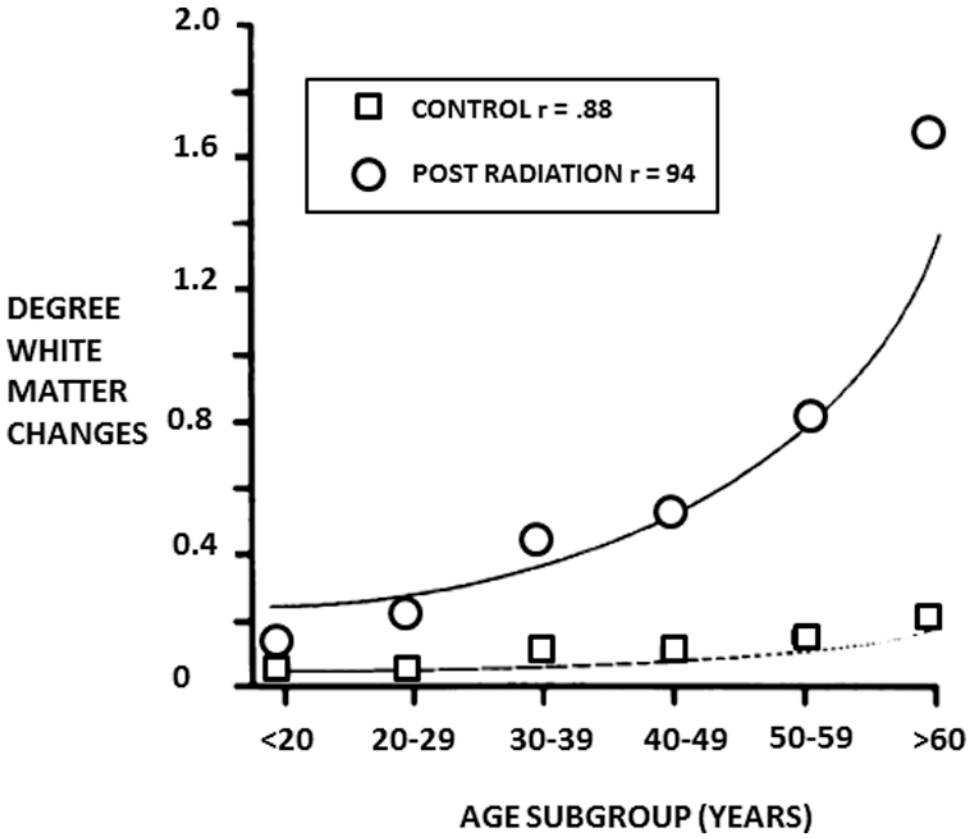

Figure 5. The severity of radiation induced white matter damage increases with age

Graph of the average degree of supratentorial white matter changes versus age. Therapeutic and controls groups are included, the curves were fitted and correlation calculated using second-order polynomial regression. Taken from Tsuruda et al (*AJR* 149:165-171, 1987)[77]. Used with permission.

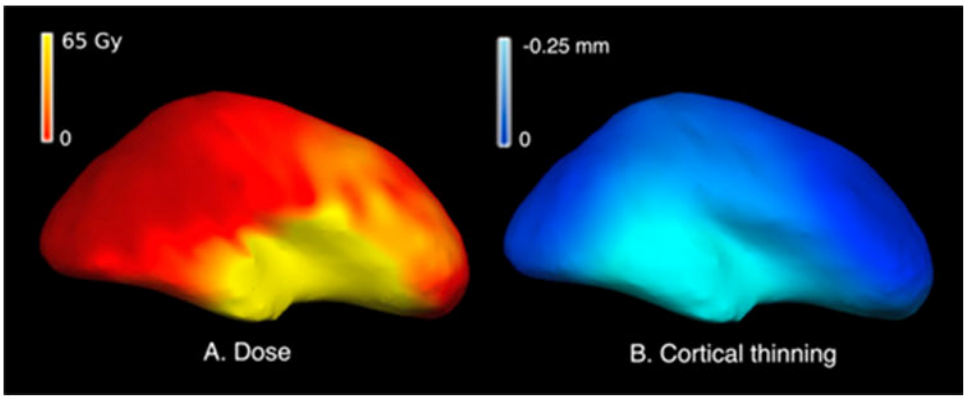

Figure 6. Cortical thinning according to dose at one year post-irradiation

Cortical surface representation of **(A)** radiation dose in Gy and **(B)** cortical thinning at 1 year observed in an example patient. Regions receiving a higher dose show a greater degree of cortical thinning at 1 year post radiation therapy.[132]

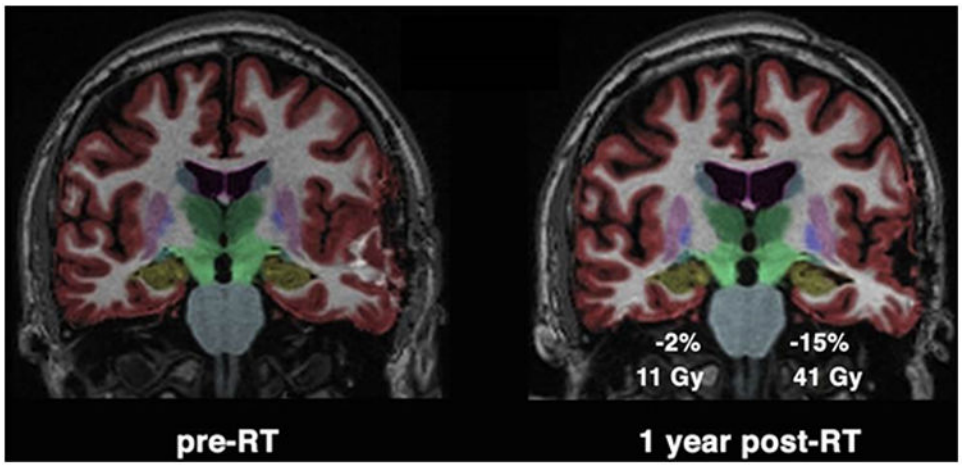

Figure 7. Radiation dose-dependent hippocampal atrophy

Coronal projection of brain MRI from a glioma patient pre-radiotherapy (pre-RT) on left, and one year post-radiotherapy (post-RT) on right. Color overlay shows automated segmentation of hippocampus in yellow. Greater percent decrease in hippocampal volume was seen in the hippocampus with higher mean dose of 41 Gy. [137]

Table 1

Evidence for White Matter Damage After Brain Irradiation

Species	Subject Stage (Adult/Pediatric/Elderly)	Radiation Dose (Gy) WBRT/ PBRT	Fraction (Gy)	Assay	White Matter Changes	Time (mos)	Reference
Human	Adult	50 – 81	1.8 or 2	DTI	Yes	1.5	Nagesh et al, 2008[148]
Human	Adult	50 - 60	1.8 or 2	Histology	Yes	-	Burger et al, 2006[170]
Human	Adult	35	2.5 or 3	MRI	Yes	11-51	Fuji et al, 2006[171]
Human	Adult	60 **tumor only**	2	DTI	**No**	6	Prust et al, 2015[131]
Human	Adult	59 - 60	1.8 or 2	DTI	Yes **	12	Connor et al, 2016[27]
Human	Adult	45-59.4	1.8	DTI	Yes **	36-108	Ravn et al, 2013[146]
Human	Pediatric	36 WB; 54 local	Typically 1.8	DTI	Yes	30	Mabbott et al, 2006[172]
Human	Elderly >60 years	50	1.8 or 2	MRI	Prevalent	38	Tsuruda et al, 1987[77]
Mouse	Adult	30	30	Histology	Yes	8	Chiang et al, 1993[173]
Rat	Adult	17.5	17.5 *	Histology	Yes	10	Calvo, et al, 1988[63,173]
Rat	Adult	45	5 *	Histology	**No**	12	Shi et al, 2009[29]
Monkey	Adult (Rhesus)	40	2 *	Histology	**No**	6, 12	Nakagaki et al, 1976[188]
Monkey	Adult (Rhesus)	60	2	Histology	Yes	6, 12	Nakagaki et al, 1976[188]
Monkey	Adult (Rhesus)	80	2	Histology	Yes	6, 12	Nakagaki et al, 1976[188]

WBRT = whole brain irradiation
PBRT = partial brain irradiation
DTI = diffusion tensor imaging
MRI = magnetic resonance imaging

* Note apparent effect of dose rate; according to histology low dose rate avoided white matter abnormalities, despite cognitive deficits in this model and with this dosing schedule.

** Very low total doses elicited white matter DTI changes.