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Radiation Toxicity in the Central Nervous System: Mechanisms and Strategies for Injury Reduction

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The potential for radiation-induced toxicities in the brain produces significant anxiety, both among patients receiving radiation therapy and those radiation oncologists providing treatment. These concerns often play a significant role in the medical decision-making process for most patients with diseases in which radiotherapy may be a treatment consideration. Although the precise mechanisms of neurotoxicity and neurodegeneration after ionizing radiation exposure continue to be poorly understood from a biological perspective, there is an increasing body of scientific and clinical literature that is producing a better understanding of how radiation causes brain injury; factors that determine whether toxicities occur; and potential preventative, treatment, and mitigation strategies for patients at high risk or with symptoms of injury. This review will focus primarily on injuries and biological processes described in mature brain.

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Radiobiology of Therapeutic Radiation on the Central Nervous System

All forms of ionizing radiation, ranging from nearly weightless photons to heavy charged particles such as protons or carbon ions, have the potential to produce toxicity in the central nervous system (CNS). Ionizing radiation particles have in common the physical ability to generate free radicals that may cause direct or indirect DNA damage, but may also provide a source of metabolic stress to which the CNS is particularly susceptible as compared to other tissue types.[1,2] Although the fixation of double-stranded DNA breaks leading to mitotic catastrophe is the most supported mechanism of radiation-induced cell death,[3] it is thought to be more relevant in cells undergoing active cell division. In normal mature CNS where mitotic potential is limited, there is growing evidence to suggest that other mechanisms of radiation-induced damage, such as oxidation of the lipid bilayer,[4] changes in microvascular permeability, cell-cell junctional complex rearrangements,[5] and mitochondrial alterations inducing additional oxidative stress,[6] are likely more important subcellular targets for ionizing radiation. Through the combination of DNA damage and subcellular alterations, radiation has the capacity to alter tumor microenvironment, cellular architecture, permeability of tumor vasculature, and permeation of drugs within the CNS, which have the potential to simultaneously augment as well as reduce the toxicities induced by radiation treatment.

Larger fraction sizes and compressed fractionation schedules are believed to contribute disproportionately to toxicity of normal tissues in the CNS. The Radiation Therapy Oncology Group (RTOG) prospectively compared randomized whole-brain radiation fractionation schedules in patients with symptomatic brain metastases to determine impact on survival.[7] Multiple regimens tested ranged from 10 Gy in a single fraction to up to 40 Gy delivered over 20 fractions. Although there was not an appreciable difference in survival with most fractionation schedules, the delivery of 10 Gy in a single treatment to the entire brain was determined to be significantly detrimental to survival. These data suggested that above a certain threshold, large fraction sizes produce worse toxicity in the brain when treatment volumes are equivalent.

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Likewise, in a retrospective evaluation of patients receiving whole-brain radiotherapy for brain metastases, toxicity was observed at 20.6 months in patients who received greater than 3 Gy per fraction, many of whom also received concurrent radiosensitizing chemotherapy. More importantly, no dementia was detected in patients who received 3 Gy or less per fraction.[8] Subsequent evaluations suggested that reduced fraction sizes were recommended for better-performing patients with a longer anticipated life expectancy when the entire brain required radiation treatment.[9]

As a consequence, therapeutic treatment regimens engineered to limit the amount of treated normal tissue have gained in popularity based on the hypothesis that a reduced treatment volume yields fewer and less severe toxicities. Because radiation delivery techniques such as stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy deliver ablative doses of radiation, their practical use is of benefit in limited situations to treat well-circumscribed targets that are spatially located at sufficient distance from critical structures. RTOG 90-05 defined the tolerance of SRS dosing in a volumetric fashion. As the diameter of the target lesion increased to greater than 2 cm, the tolerated dose decreased from 24 Gy to 15 Gy when the lesion diameter was greater than 3 cm,[10] and was limited by severe edema and the development of radionecrosis at a median follow-up of 3 years. When SRS was combined with whole-brain radiation, thereby increasing the total dose, side effects of nausea as well as central and peripheral neurologic toxicities occurred more frequently and was more severe within 90 days of radiation treatment.[11] Unfortunately, the use of limited radiation treatment volumes has most often been used as a tool to extend local control, not with the anticipation of the overall cure of the patient.

Although the toxic effects of radiation depend on total dose, fractionation schedule, and volume treated, there is evidence to suggest that differential radiation sensitivity exists within various CNS subcompartments. Neurogenesis, a process by which new neurons are produced in the brain, persists throughout life in discrete regions of the adult brain, including the hippocampus. It has long been established that radiation exposure has a negative impact on neurogenesis.[12-14] It is believed that these disruptions in neurogenesis and hippocampal function are directly linked to cognitive and mood disruptions observed in patients.[15,16] However, what is less well understood is to what extent spontaneous recovery of neurogenesis and hippocampal function is possible, the time course for any potential recovery, the effects of age and preexisting neurologic disease, and what therapies and interventions might benefit functional recovery.

Acute vs Late Effects of Radiotherapy

The etiology of CNS dysfunction in patients after irradiation is multifactorial,[17,18] influenced by individual factors including age, medical comorbidities, psychological and genetic predispositions, characteristics of any underlying malignancy, and any additional injuries caused by other treatment modalities such as surgery and chemotherapy. From a radiobiological perspective, radiation-induced brain injury is described in 3 phases—acute (within days to weeks after irradiation), early-delayed (within 1-6 months postirradiation) and late (>6 months postirradiation).[19] From the clinical perspective, the RTOG defined acute toxicity for CNS as those symptoms attributable to radiation treatment and occurring during and within 90 days of radiation treatment, which include neurologic changes requiring corticosteroids, seizure, coma, and paralysis. Late toxicities occur after 90 days and include headache, lethargy, severe CNS dysfunction including partial loss of power and dyskinesia, and coma.[20] Because of the limited lifespan of many adult patients receiving radiation treatment to the CNS, it is largely unknown what the long-term consequences of most treatments would be after many years. Both conventional and more precise radiation treatment modes have the potential to produce side effects such as fatigue, cognitive alterations in short-term memory and concentration, pituitary dysfunction resulting in endocrinological disruptions, and in rare cases, dementia.[9,21-23] Thus, the goals of radiation toxicity research include improved efforts at enhancing efficacy and reducing side effects.

Radiation-induced neuropsychological function and cognition deficits evolve in a biphasic pattern with a subacute transient decline corresponding to more common symptoms, followed by a late-delayed irreversible impairment several months or years later in a much smaller proportion of surviving patients.[24] Concerns regarding the toxicity of treatment have to be balanced with data suggesting that uncontrolled tumor in the CNS has the most severe toxicities, well above those observed with radiation.[25] Indeed, the modality of treatment for some patients, that is, palliative vs more aggressive treatment, may reflect an inherent bias toward an improved baseline functional well-being in patients receiving more aggressive treatments as determined by FACT-Br (Functional Assessment of Cancer Therapy-Brain) scores.[26]

Functional toxicities are believed to be correlated to observed changes in the entire brain, including gray matter, white matter, ventricles, and combinations among them.[27,28] Hallmarks of normal tissue toxicity include vascular injury.[29] Radiation primarily causes coagulation necrosis of the white matter tracts and cerebral vasculature by axonal demyelination and damage to vascular endothelial cells.[30] Leukoencephalopathy occurs from the overproduction of myelin in oligodendrocytes and occurs as a late toxicity (Fig. 1A). Demyelination can also occur in spinal cord and nerve roots. Neurodegeneration may occur directly from radiation-induced stress as well as from a by-product of detrimental effects on the supporting astrocytes, and supporting astrocytes may undergo reactive gliosis. However, the most severe form of injury is radionecrosis, producing a brisk neuroinflammatory reaction (Fig. 1B). Neuroinflammation is a prominent feature of many CNS diseases including stroke, Alzheimer disease, Parkinson disease, and mild cognitive impairment, and it has also been hypothesized to contribute to radiation-induced cognitive losses.[15,31,32]