Radiation-induced brain injury: low-hanging fruit for neuroregeneration

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Brain radiation is a fundamental tool in neurooncology to improve local tumor control, but it leads to profound and progressive impairments in cognitive function. Increased attention to quality of life in neurooncology has accelerated efforts to understand and ameliorate radiation-induced cognitive sequelae. Such progress has coincided with a new understanding of the role of CNS progenitor cell populations in normal cognition and in their potential utility for the treatment of neurological diseases. The irradiated brain exhibits a host of biochemical and cellular derangements, including loss of endogenous neurogenesis, demyelination, and ablation of endogenous oligodendrocyte progenitor cells. These changes, in combination with a state of chronic neuroinflammation, underlie impairments in memory, attention, executive function, and acquisition of motor and language skills. Animal models of radiation-induced brain injury have demonstrated a robust capacity of both neural stem cells and oligodendrocyte progenitor cells to restore cognitive function after brain irradiation, likely through a combination of cell replacement and trophic effects. Oligodendrocyte progenitor cells exhibit a remarkable capacity to migrate, integrate, and functionally remyelinate damaged white matter tracts in a variety of preclinical models. The authors here critically address the opportunities and challenges in translating regenerative cell therapies from rodents to humans. Although valiant attempts to translate neuroprotective therapies in recent decades have almost uniformly failed, the authors make the case that harnessing human radiation-induced brain injury as a scientific tool represents a unique opportunity to both successfully translate a neuroregenerative therapy and to acquire tools to facilitate future restorative therapies for human traumatic and degenerative diseases of the central nervous system.

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ALTHOUGH brain radiation therapy is critical to the management of primary and metastatic brain tumors, cognitive impairments caused by chemotherapy and radiation are increasingly recognized. In adults, impairments occur in up to 50%–90% of patients within 3–6 months after fractionated whole-brain radiation therapy (WBRT).^{8,24} Long-term survivors of childhood brain radiotherapy are most severely affected, experiencing double-digit declines in IQ, vocational restriction, and an elevated incidence of psychiatric impair-

ments.^{45,52,53} Neurooncology outcomes have historically focused on survival. However, as outcomes have progressively improved for several malignancies, there has been an increasing need to preserve and improve the quality of life, not just overall survival. As perhaps the most severe and widespread form of iatrogenic brain injury, much remains to be learned about radiation-induced brain injury—the cognitive price of prolonged survival. Excitingly, compelling prospects exist to not only better understand human CNS pathophysiology through this condition, but

ABBREVIATIONS BrdU = bromodeoxyuridine; ESC = embryonic stem cell; IMRT = intensity-modulated radiation therapy; NSC = neural stem cell; OPC = oligodendrocyte progenitor cell; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

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to provide meaningful regenerative therapies to those who have battled with brain tumors and lived to suffer the long-term consequences of current treatments.

Multiple Paths to Radiation-Induced Brain Injury

Of the various forms of radiotherapy, WBRT carries the greatest risk of iatrogenic cognitive impairment. Although it was once administered prophylactically to those with childhood leukemia, WBRT has increasingly become a judiciously administered therapy in children since the realization of its devastating cognitive consequences. The adult brain has historically been considered relatively refractory to WBRT, which is administered to roughly 200,000 cancer patients per year.⁷¹ Increasing recognition of the cognitive toll incurred by adults following WBRT is now prompting critical reevaluation of the role of WBRT in adults with brain metastases.⁷

At the other extreme, stereotactic radiosurgery (SRS) minimizes off-target radiation exposure, serving as an adjunct to or alternative for discrete resections. Given the minimally invasive nature of SRS, and its ability to treat new additional new lesions over time, SRS, in combination with close follow-up, may increasingly enable avoidance of up-front WBRT in patients with brain metastases.⁷ The higher focal doses of radiation employed with SRS, however, are not entirely without consequence. In a recent consecutive series of 271 brain metastases treated with stereotactic radiosurgery, follow-up examination, at a median of 17.2 months, revealed radionecrosis in 25.8% of patients, two-thirds of whom were symptomatic. The incidence of radionecrosis in those followed up out to 24 months was 34%.³⁷ Although not the focus of this review, much remains to be learned about the pathophysiology of radionecrosis, a severe, albeit focal form of radiation-induced brain injury.

Intensity-modulated radiation therapy (IMRT) provides broader radiation coverage than SRS but can be contoured to spatially tailor the radiation field. Given the particularly critical role of the hippocampus and hippocampal stem cells for learning and memory, and the sensitivity of this region to radiation, IMRT has recently been used to perform hippocampus-avoiding WBRT in an attempt to minimize cognitive dysfunction.²³ Importantly, radiation therapy for skull base tumors via IMRT and proton-beam radiotherapy can also yield substantial radiation doses to the nearby temporal lobe, inducing parenchymal injury and cognitive impairment.^{15,55}

Mechanisms of Radiation-Induced Brain Injury

Cytotoxicity and Neuroinflammation

Radiation deposits energy into cellular biomolecules, producing chemical changes including DNA damage. Radiolysis of water generates reactive oxygen species, which are potentially amplified via radiation-induced damage to energy-producing mitochondria, leading then to further damage of cellular nucleic acids, proteins, and lipids, as well as components of the extracellular matrix.³⁸ Local

tissue injury prompts activation of microglia, the effector cells of the brain's innate immune system.^{21,56} An initial wave of acute radiation-induced microglial activation and neuroinflammation is then followed by a persistently activated microglial state that may last for decades.⁵⁹ Activated microglia secrete inflammatory cytokines and produce reactive oxygen species, potentially thereby serving to propagate an ongoing cascade of chronic neuroinflammation—one that has been correlated with impairments in hippocampal neurogenesis and cognitive function.^{29,39,57} We recently demonstrated that the transcriptional profile of radiated microglia closely mirrors that acquired by microglia during aging⁴²—itself the single greatest risk factor for cognitive decline and neurodegenerative disease.

Impact of Radiation on Neurogenesis and Neuronal Function

Mounting evidence in recent years has linked hippocampal neurogenesis with cognitive functions including learning, memory, and spatial navigation.^{48,70,72} Indeed, the profound impact of brain irradiation on neurogenesis has led to its becoming the gold-standard laboratory technique to abolish neurogenesis in animal models.^{4,56,57,83,96} Although the mechanisms are not fully understood, a link between persistent microglial activation and impaired hippocampal neurogenesis has been reported.^{57,58} It is now known that although radiation kills rapidly dividing neural progenitor cells, the more quiescent neural stem cells (NSCs) remain viable after brain radiation, albeit in a persistently quiescent state only modestly responsive to proneurogenic stimuli such as voluntary physical exercise and mitogenic stimulation.^{60,93} Unfortunately, radiation's failure to kill quiescent NSCs mirrors its inability to kill quiescent glioma stem cells, which reestablish a typically more aggressive and resistant recurrent malignancy.

As a model, radiation-induced ablation of neurogenesis was previously used specifically to illustrate the importance of neurogenesis to cognition.^{54,74,75} However, radiation is now known to impact the spectrum of CNS cell types, including neurons themselves that manifest altered synaptic morphology, function, and plasticity.^{34,46,73,89} Of particular therapeutic relevance are the effects of radiation on the oligodendrocytic lineage.

Radiation and White Matter Degeneration

Progressive white matter “atrophy” is a hallmark of radiation-induced brain injury.⁸⁶ Oligodendrocytes are exquisitely sensitive to radiation due in part to their high metabolic demand and mitochondrial content, leaving them susceptible to oxidative stress and bioenergetic failure.³² Superimposed microvascular injury has also been implicated in both delayed white matter injury and radiation necrosis.^{14,62,95} In contrast to other mechanisms of demyelination, surviving endogenous progenitor cells are intrinsically dysfunctional following radiation, impeding the usual reparative responses of NSCs and oligodendrocyte progenitor cells (OPCs). As such, radiation results in a pervasive pattern of OPC loss and progressive demyelination that has been well characterized in rodents and humans.⁶⁵ Given the particular importance of white

matter in cognitive tasks of working memory and executive function, diffuse white matter degeneration is a major contributor to radiation-induced cognitive impairment. Although this review focuses on the effects of radiation on oligodendrocyte progenitor cells, it should be noted that OPC function is additionally impaired by certain chemotherapeutic agents,^{26,30} the combinatorial effects of which further exacerbate white matter atrophy following treatment of brain tumors.

White Matter as a Target for Regeneration

Myelin: A Dynamic and Resilient Contributor to Cognition

Axons within CNS white matter tracts depend on myelin for function and long-term survival.⁶⁸ Increasing evidence reveals a dynamic cross-talk between neurons, oligodendrocytes, and OPCs, with white matter “plasticity” now understood to be integral to cognitive function.^{22,51,69} Several diseases affect white matter, ranging from multiple sclerosis to childhood leukodystrophies, and have prompted development of several animal models of demyelination. One such genetic model of oligodendrocyte ablation revealed acute axonal injury even preceding ultrastructurally detectable loss of myelin membranes, illustrating the dependence of neurons on functional oligodendrocytes.⁶³ Nevertheless, most forms of acute demyelination, including toxin-induced demyelination, are followed by generation of new oligodendrocytes by local white matter OPCs and subventricular zone NSC-derived OPCs. These swiftly remyelinate the lesioned area, averting permanent axonal injury.⁶⁶ Encouragingly, adult animal models of even widespread oligodendrocyte loss—arguably more “severe” than that seen in human patients after radiation-induced brain injury⁶⁵—reveal that surviving healthy OPCs *can* efficiently and effectively remyelinate denuded axons throughout the brain.⁸⁸ Moreover, self-regulation of OPC number and distribution throughout the brain appears hardwired into the very identity of OPCs, such that any number of experimental strategies to remove them from the brain either during or after development is met with remarkably swift and complete proliferation and migration of remaining OPCs to restore normal numbers and distribution throughout the brain.^{5,35} Given these potent regenerative capabilities, OPCs represent a promising avenue for treatment of radiation-induced brain injury.

Cell Therapies for Radiation-Induced Brain Injury: Proof of Principle

Although endogenous OPCs are rendered dysfunctional and unable to proliferate by brain radiation, healthy functioning exogenous OPCs maintain their normal function upon implantation into a previously irradiated brain or spinal cord, where they can migrate widely, generate oligodendrocytes, and remyelinate lesioned areas.^{19,20,31} In the 1990s, Franklin et al. noted that implanted OPCs could engraft into the spinal cord following either chemical- or radiation-induced demyelination, though they were unable to traverse areas of normal nonradiated tissue to reach areas of radiation or focal demyelination.^{19,20} In fact, remyelination by grafted cells was only observed in regions *completely* devoid of endogenous OPCs.²⁸ Conversely, Monje

et al. in 2002 grafted bromodeoxyuridine (BrdU)-labeled NSCs into irradiated rat brains and found relatively poor survival of transplanted cells and lower rates of neuronal differentiation in the irradiated, relative to the nonirradiated, microenvironment.⁵⁷ Interpretation of these data is tricky, since most cells die after transplantation, and BrdU was subsequently found able to be recycled from dead transplanted cells to be taken up by endogenous dividing cells in the area.¹⁰ As such, the apparently poor survival of NSCs in the irradiated hippocampus may have simply reflected the lower rates of endogenous neurogenesis following brain irradiation.⁵⁷ Irvine and Blakemore in 2007 grafted early passage neurospheres from an E14 GFP-labeled mouse into the lateral ventricles of mice lesioned with 40 Gy of x-irradiation. Fourteen days later, grafted GFP-positive cells were widely distributed in areas of significant radiation-induced injury wherein the endogenous NG2-positive OPCs had been fully ablated. However, no engraftment was seen in regions with surviving OPCs.³¹ Consistent with this, Niranjana et al. found that survival of grafted mouse NSCs could be improved by WBRT (20 or 40 Gy) 7 days before cell injection.⁶¹ In further support of cell transplantation, models of local demyelination demonstrated several-fold faster and more complete remyelination with exogenous cell delivery than could occur by replying upon adjacent surviving OPCs.⁶

Preclinical Cognitive Benefits

In 2009 and 2011, Acharya et al. performed the first studies aimed specifically at evaluating the role of grafted cells for treating radiation-induced cognitive impairment in rats, using human embryonic stem cells (ESCs) and human NSCs, respectively.^{2,3} In both reports, cells were injected into the hippocampus 2 days after delivering a 10-Gy dose of whole-brain radiation, yielding improved performance on hippocampus-dependent cognitive tasks. Although evidence of surviving cells was provided via human nuclei staining at 1 month after transplantation, claims of neural differentiation were supported only by colocalization of neuronal markers with BrdU, which may again have reflected endogenous neurogenesis. Indeed, we recently observed that GFP-labeled ESC-derived NPCs injected into the irradiated mouse hippocampus not only generated a small number of new graft-derived neurons, but also ameliorated local levels of endogenous neurogenesis via presumably trophic effects (TC Burns, unpublished observations). As such, implanted NSCs may augment cognition following brain irradiation by helping to replenish endogenous OPCs and enhancing endogenous hippocampal neurogenesis, among other as yet ill-defined trophic mechanisms.

In 2015, Piao et al. used human ESC-derived OPCs in a rat model treated with a clinically relevant regimen of 40 Gy of fractionated radiation. As predicted from the aforementioned studies, the healthy, nonirradiated OPCs migrated widely from their points of implantation to broadly remyelinate the CNS. Interestingly, implanted OPCs yielded cognitive recovery when implanted into the forebrain, whereas injections into the cerebellum prompted motor recovery.⁶⁷ Given that radiation-induced brain injury yields a broad array of pathological changes spanning endothe-

lium, microglia, and neuronal synapses, as well as OPCs, observations of a single cellular intervention (OPCs), which yields remarkable levels of functional recovery approximating performance of nonirradiated animals, portends optimism that other potentially secondary cellular changes may be mitigated by restoration of OPCs and myelin function. Alternatively, OPCs, may also possess trophic and supportive functions in similar manner to NSCs, such as ability to modulate inflammation, secrete neuroprotective compounds, promote endogenous neurogenesis augment neuronal plasticity.^{12,85} As such, OPC transplantation may mediate behavioral recovery via multiple synergistic actions of cell replacement, avoiding secondary cellular changes consequent to myelin and OPC loss, as well as potentially a plethora of other trophic mechanisms.

Which Cell Types for Human Trials?

Primary OPCs have been evaluated in preclinical models of several diseases, including multiple sclerosis, childhood hypomyelinating disorders, traumatic brain injury, and stroke among others.⁹⁴ In a Geron-sponsored trial for spinal cord injury, ESC-derived OPCs became the world's first ESC-derived cell product to be used in a human clinical trial. Despite evidence of safety, the study was terminated prematurely for financial reasons.^{18,79} OPCs seem particularly well suited to radiation-induced brain injury, given the inherent demyelinating process, the widespread loss of endogenous OPCs, and remarkable migratory behavior of transplanted OPCs following radiation-induced depletion of endogenous progenitors in animal models.

A well-characterized line of fetal-derived NSCs was employed for a Phase I clinical trial for Pelizaeus-Merzbacher disease, a rare childhood leukodystrophy; MRI findings from these patients provided the first human in vivo evidence of stem cell-derived myelin production.²⁵ As such, since NSCs also differentiate into OPCs that generate myelin in vivo after experimental brain irradiation, improve cognitive function in animal models of brain radiation,^{2,3} and demonstrate a host of well-documented trophic effects, NSCs and OPCs may both represent appropriate candidates for clinical trials of radiation-induced brain injury.

OPCs and NSCs may be derived from either fetal brains or ESCs. Additionally, the feasibility of generating induced pluripotent stem cell-derived cells for transplantation offers the potential to avoid immunosuppression, an increasingly relevant consideration given the emerging promise of novel immunotherapies for primary and metastatic brain tumors.

Potential Pitfalls and Challenges

Cell Distribution in the Human Brain

One of the major challenges to translation of rodent to human studies for neuroregeneration is the sheer size of the human brain. While systemically delivered (intravenous or intraarterial) therapies are easily scaled by increasing cell numbers, and, focal targeted therapies for stroke or Parkinson's disease are feasible with multiple needle passes to the relatively small affected area, the prospect of treating an entire human brain is rather

more daunting. While a few millimeters of cell migration from the site of implantation may be sufficient to broadly remyelinate a mouse brain,^{82,90,92} the human brain is over 3000 times the size of a mouse brain. As such almost epic migratory feats would be required to achieve more than paltry benefit. Fortunately, the very presence of prior radiation is well documented to promote migration and wide distribution of implanted OPCs in the CNS. Nevertheless, preclinical work in rats suggested that cells implanted into the forebrain failed to migrate into the cerebellum and vice versa.⁶⁷ Such data suggest finite limits to migratory capacity, increasing the probability of requiring multiple delivery sites in a human subjects. Although the very biology of OPCs provides reason to be optimistic that they will proliferate in vivo and achieve increasingly broad and uniform distribution after implantation, only pilot clinical trials in humans will enable this question to be adequately answered.

Unique Properties of Human White Matter

Rodent OPCs proliferate throughout life, and new OPC-derived oligodendrocytes contribute actively to cognitive function.^{22,50} White matter is also dynamically regulated in humans, with increased local fractional anisotropy detected in adult subjects after training in a complex visuomotor task⁷⁸ or learning a second language.⁷⁷ However, in contrast to mice, radiocarbon dating of cells in the human brain has indicated that very few human oligodendrocytes are born after early childhood.⁹⁷ These data suggest that adult human white matter plasticity occurs at the level of postmitotic oligodendrocytes rather than via generation of new oligodendrocytes from endogenous OPCs, as has been documented in rodents.²² Whether this apparent species-specific variability in adult white matter plasticity could impede human remyelination from implanted OPCs after radiation injury will need to be established empirically. However, given that human OPCs engage in some degree of remyelination in the early stages of multiple sclerosis, and can successfully remyelinate an entire mammalian brain in xenograft studies, strong proof of principle points to remyelinating OPCs successfully engrafting into the vacated OPC niche following human brain irradiation.

Could Progenitor Cells Poke the Sleeping Dragon?

A dynamic tension exists between neurooncology and neuroregeneration. Whereas neuroregenerative strategies may promote cell survival, proliferation and migration, malignant brain tumors are themselves the product of *excessive* cell survival, proliferation, and migration. Could introducing these "ingredients of malignancy" into a brain already afflicted with neoplasia be the equivalent of poking the proverbial sleeping dragon? Tumorigenesis is already perhaps the single greatest risk of regenerative strategies, with cell therapies, with avenues to tumorigenesis including teratomas from residual undifferentiated pluripotent (ESCs and induced pluripotent stem cells), malignant transformation of in vitro cultured cell lines, and even epigenetic drift of cultured cells into a more primitive germ cell-like state.^{41,44} While vigilance to avoid direct graft-induced tumorigenesis is obviously paramount,

could implanted cells also secrete a cocktail of trophic and proangiogenic molecules^{11,13} that could reactivate residual or dormant tumor cells in the previously irradiated patient? Vigilant monitoring for neoplasia of any type, be it recurrent or graft derived, with serial imaging or biomarkers will be absolutely critical in neuroregenerative trials for radiation-induced brain injury. We speculate that such risks may be lower with cellular therapies than with strategies aiming to “reactivate” endogenous progenitors via growth factor infusion, as has been considered for other CNS diseases.^{76,98} In fact, NSCs themselves exhibit innate antitumor properties.⁸⁴ Given the migratory capacity of OPCs throughout previously irradiated brain, and the tropism of many progenitor cell types for tumors,^{1,17,43,87} OPCs or NSCs engineered to additionally produce antitumor and/or proregenerative molecules may enable broad delivery of protective and regenerative cells throughout irradiated portions of the CNS. In this manner, neurooncology patients in the future may receive therapies designed to be simultaneously regenerative and antineoplastic, not only restoring white matter but remaining in place to secrete antineoplastic compounds and serve as sentinel first responders in the event of recurrent disease.

A Word of Caution Regarding Glioma Immunotherapies

Glioma stem cells are of increasing interest as a target for novel immunotherapeutic strategies.^{33,47,81} Given the very close relationship between glioma stem cells and endogenous progenitor cells, strategies immunologically targeting specific markers of NSCs and OPCs present tempting targets to achieve oncological control in primary brain tumors.²⁷ However, preclinical models have demonstrated an appropriately trained immune system of being quite capable of entirely ablating endogenous OPCs.⁴⁰ While this strategy may provide a valuable opportunity to functionally interrogate the roles of OPCs in preclinical models, active immunization against molecules expressed by endogenous stem or progenitor cells will predictably lead to patients suffering from the resultant cognitive effects of ablated progenitor populations. Moreover, such patients would, from that point forward, rapidly reject any therapeutically implanted progenitor cells, making the resultant cognitive deficits irreversible.

Work in Progress

Once a decision has been made to proceed with clinical translation, innumerable perhaps mundane but critical questions arise, often requiring educated guesses in light of practical differences between humans and preclinical rodents. Some questions, for example, are as follows: What are the appropriate inclusion/exclusion criteria? What type and origin of cells should be used—autologous or allogeneic? How many cells are needed in the larger human brain? When after injury should they be delivered? What is the optimal site(s) of delivery? What adjuvant therapies would facilitate optimal survival, integration, and function? Should label(s) be considered for subsequent detection via MRI or postmortem histology?

Behind optimizing each of these decisions is the motivation to detect a meaningful biological response in a

“positive” trial, which is often in large part dependent on selecting the appropriate outcome measure. Perhaps more important than a given trial being “positive,” however, is the data gained from even incompletely successful outcomes. Fortunately, the quantity and quality of biological data obtainable that can be incorporated into such trials is increasing exponentially. Brain tumor mutations can now be detected in the cell-free DNA of cerebrospinal fluid.^{64,91} In a recent proof-of-principle study, elevated cell-free RNA transcripts of APP and PSD3 were identified in the serum of patients diagnosed with Alzheimer’s disease, while transcripts associated with neural development were detectable in peripheral blood of women during pregnancy.³⁶ Plasma phospholipid profiles can now identify patients expected to develop age-related memory impairment within 2–3 years, with over 90% accuracy.⁴⁹ Such techniques, in combination with cell-type specific transcriptome analysis of CNS samples from previously irradiated patients at time of surgery,^{16,42,99} may enable unprecedented windows into human CNS pathophysiology and responses to putative therapies.

Unique Advantages of Radiation Injury for Translational Neuroregeneration

Radiation-induced brain injury offers unparalleled opportunity to study human CNS disease, regardless of the proposed therapy under consideration. In virtually no other CNS disease can the patient be studied prior to, during, and after injury in a longitudinal and even scheduled manner. Stroke, spinal cord injury, and traumatic brain injury literature abound with neuroprotective compounds that are most effective when given prior to the actual injury. Of course, progenitor cells should be administered only after radiation to avoid damage to the implanted cells by the radiation. Moreover, certain other therapies such as antioxidants could conceivably reduce radiation efficacy if administered prior to radiation. Nevertheless, the availability of this coveted “preinjury” window of opportunity sets radiation-induced brain injury apart from other CNS injuries and diseases as an ideal candidate for trials of appropriate neuroprotective agents, ideally in conjunction with systematic acquisition of detailed baseline and longitudinal outcomes data.

Traumatic brain injury, spinal cord injury, and stroke are notoriously heterogeneous. Even most neurodegenerative diseases vary widely in severity and rate of progression. Radiation-induced brain injury offers an uncommon opportunity to study the efficacy of a neuroprotective or neuroregenerative therapy in patients who all receive the identical lesion in a virtually identical manner. Moreover, in contrast to spinal cord injury—the only condition yet treated with OPCs, and which occurs in approximately 12,000 patients per year—WBRT is currently administered to roughly 200,000 patients per year in the United States, greatly enhancing the feasibility of clinical trials.

Much of the failure to develop effective therapies for CNS disease has been attributed to preclinical studies being predominantly focused upon animal models that poorly replicate human disease. To date, for example, no transcriptome data exist in public databases for human CNS

tissue following stroke, traumatic brain injury, or spinal cord injury, although such data abound for mice and rats. Previously irradiated brain tissue is surgically accessible at the margin of tumor resections, in both a delayed manner for recurrent disease and acutely in the case of neoadjuvant radiation therapy, providing unprecedented opportunities to study and understand the human pathophysiological responses to CNS injury. Indeed, remarkable overlap exists between neurological and inflammatory diseases within species, allowing extrapolations that are impossible across different species.^{9,80} That is to say, the transcriptome of human traumatic brain injury is likely much more closely related to human radiation injury than it is to mouse traumatic brain injury. As such, insights gained in the course of developing therapies for human radiation-induced brain injury may provide exceptional insights into human CNS aging, traumatic injury, and neurodegeneration.^{9,42}

Unfortunately, most patients with metastatic tumors to the CNS die of their malignancy within 2 years from diagnosis of CNS involvement. Since cognitive deficits may present within 3 months of brain radiation, and experimental regenerative therapies may be employed to enhance cognition and quality of remaining life despite the likelihood of recurrent systemic disease, autopsy tissue may frequently become available for the assessment of outcomes and refinement of methodologies within a shorter time frame than for almost any other neurological disease. Though a stark reminder of the work ahead to improve cancer treatments, such direct and timely access to the brains of those treated with regenerative therapies will be invaluable for iterative advances toward more effective therapies in the future.

Conclusions

In 1928 Ramón y Cajal wrote in his book *Degeneration and Regeneration of the Nervous System*: “In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree.” We now have sufficient evidence that this harsh decree *can* be changed and argue that radiation-induced brain injury offers low-hanging fruit to realize Cajal’s “science of the future.”

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