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Preclinical MRI: Studies of the irradiated brain

Joel R. Garbow [a,b,*], Christina I. Tsien [c], Scott C. Beeman [a]

[a] Department of Radiology, Washington University, Saint Louis, MO, United States
[b] The Alvin J. Siteman Cancer Center, Washington University, Saint Louis, MO, United States
[c] Department of Radiation Oncology, Washington University, Saint Louis, MO, United States

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ABSTRACT

Radiation therapy (RT) plays a central role in the treatment of primary brain tumors. However, despite recent advances in RT treatment, local recurrences following therapy remain common. Radiation necrosis (RN) is a severe, late complication of radiation therapy in the brain. RN is a serious clinical problem often associated with devastating neurologic complications. Therapeutic strategies, including neuroprotectants, have been described, but have not been widely translated in routine clinical use. We have developed a mouse model that recapitulates all of the major pathologic features of late-onset RN for the purposes of characterizing the basic pathogenesis of RN, identifying non-invasive (imaging) biomarkers of RN that might allow for the radiologic discernment of tumor and RN, systematic testing of tumor and RN therapeutics, and exploring the complex interplay between RN pathogenesis and tumor recurrence. Herein, we describe the fundamental clinical challenges associated with RN and the progress made towards addressing these challenges by combining our novel mouse model of late-onset RN and magnetic resonance imaging (MRI). MRI techniques discussed include conventional T1- and T2-weighted imaging, diffusion-weighted imaging, magnetization transfer, and measures of tissue oxygenation. Studies of RN mitigation and neuroprotection are described, including the use of anti-VEGF antibodies, and inhibitors of GSK-3β, HIF-1α, and CXCR4. We conclude with some future perspectives on the irradiated brain and the study and treatment of recurrent tumor growing in an irradiated tumor microenvironment.

1. Introduction

1.1. Background

The management of high-grade tumors of the central nervous system (CNS) remains a challenging clinical problem, often requiring multimodal therapy involving surgical resection, chemotherapy, and radiation (RT). Radiation therapy has traditionally played a central role in the treatment of primary brain tumors. Yet, despite recent advances in RT treatment precision, local recurrences following therapy remain common. Radiation treatment planning is a complex process involving competing considerations: treating metabolic active tumor and areas of microscopic disease, while minimizing dose to critical structures and normal brain.

Radiation necrosis (RN) is a severe, late complication of RT in the brain. Factors associated with increased risk of RN include total RT dose, RT dose per fraction, total treatment volume, and use of concurrent chemotherapy. The incidence of RN following radiotherapy is on the rise, with the increased use of concurrent chemotherapy and other novel therapeutic agents with radiation sensitizing effects [1]. The onset of RN typically occurs 6 or more months following conventional fractionated RT or single-fraction stereotactic radiosurgery. RN is a substantial clinical problem often associated with devastating neurologic complications. RN is, therefore, a significant obstacle to safely delivering higher RT doses to areas of disease to improve local control.

Clinical symptoms from damage to normal brain following therapeutic radiation can include cognitive decline following whole-brain RT treatment and focal neurologic deficits associated with RN. Patients who develop clinically significant side effects from RT have limited therapeutic options. Therapeutic strategies, including neuroprotectants, have been described, but have not been widely translated in routine clinical use [2]. When clinically significant focal radiation necrosis develops, interventions, including treatment with steroids and surgical resection, may be required. Additional therapies available include anti-coagulation, pentoxifylline with Vitamin E, hyperbaric oxygen and bevacizumab.

Detailed characterization of RN, including the factors that influence its onset and progression, and identification of imaging

* Corresponding author at: Biomedical MR Laboratory, Mallinckrodt Institute of Radiology, Washington University in St. Louis, St. Louis, MO 63110, United States.
E-mail address: garbow@wustl.edu (J.R. Garbow).

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markers that facilitate noninvasive diagnosis, would significantly and positively impact the clinical management of brain-tumor patients. Together with the identification and development of neuroprotectants to reduce the incidence of necrosis and/or therapeutics to treat necrosis once formed, such characterization will allow more aggressive radiation therapy, and minimize the need for a return to the operating room for tissue diagnosis. To these ends, we have developed a mouse model that recapitulates all of the major pathologic features of late-onset RN for the purposes of: (i) characterizing the basic pathogenesis of RN; (ii) identifying noninvasive (imaging) biomarkers of RN that might allow for the radiologic discernment of tumor and RN, pathologies which demand divergent therapies; (iii) systematic testing of tumor and RN therapeutics, and (iv) exploring the complex interplay between RN pathogenesis and tumor recurrence.

Herein, we detail the fundamental clinical challenges associated with RN and summarize recent progress made towards addressing these challenges by combining our novel mouse model of late-onset RN and magnetic resonance imaging (MRI).

1.2. Clinical challenges

Accurate assessment of treatment response remains a challenge in the treatment of primary brain tumors. Standard imaging paradigms are often unable to distinguish between recurrent tumor and treatment-related changes. Pseudo progression, a phenomenon that mimics tumor progression, occurs following completion of chemo-radiation (chemo-RT) in 20–30% of GBM patients [3–7]. MR imaging following chemo-RT for brain tumor patients often demonstrates an increase in post-gadolinium, T1-weighted image intensity (contrast enhancement) and T2-weighted/FLAIR hyperintensity. Differential diagnosis includes recurrent tumor *vs.* treatment-related changes or radiation necrosis. This distinction is critical, because the appropriate therapy and prognosis differ greatly.

Imaging tools capable of distinguishing RN from recurrent tumor are lacking [8]. Several imaging groups have investigated quantitative changes in blood flow and perfusion [9–11], metabolism [11–13], and cellularity and tissue composition [13–15] following therapy to improve early, therapeutic response assessment. A critical challenge for interpreting human imaging studies of glioma is that tissue samples for confirmation of diagnosis and for biochemical characterization are frequently unavailable in patients with suspected recurrence because of the complexity and risks associated with biopsy, though Hu et al., have described such studies [16].

Given the difficulty in obtaining repeated brain biopsies, a detailed understanding of the factors that affect the onset and progression of radiation necrosis and, ultimately, its characterization by non-invasive imaging, requires the development of robust animal models that will enable clear histologic description of tissue damage in the irradiated brain. Cellular density (tissue microstructure) and vascular permeability are defining physiologic parameters that differ significantly amongst tumor, normal tissue, and radiation-damaged tissue.

1.3. Animal models of radiation necrosis

Preclinical studies have provided valuable insights into the pathogenesis of radiation-induced brain injury [17,18]. Several studies of irradiated adult rodent brain have shown: (i) marked and persistent reduction in neurogenesis [19], (ii) neuroinflammation with microglial and astrocyte activation [20], as well as (iii) progressive loss of cognitive function following single dose [21] and fractionated whole-brain irradiation (WBI) [22]. However, the lack of well-developed, small-animal models of radiation necrosis has significantly hampered the development of diagnostic and therapeutic management of cerebral RN. Until recently, reports of small-animal models of cerebral RN have been sparse, with most previous animal models developed in rats [23–25].

An optimized mouse model of cerebral RN must incorporate several important features, including: (i) consistent induction of late time-to-onset necrosis following irradiation; (ii) characteristic standard MR imaging changes (e.g., T_1- and T_2-weighted imaging) that allow clear identification of necrotic regions; (iii) tissue injury whose histology accurately matches pathological findings in brain tissue from patients with confirmed RN; (iv) progression of necrosis occurs over an experimentally appropriate period of time, thereby enabling longitudinal imaging studies to characterize the onset and development of necrosis and its response to therapeutic interventions.

Several years ago, in our laboratory, Jost et al., described a murine model of RN using a micro-radiotherapy (microRT) system [26]. More recently, Jiang et al., developed and characterized a mouse model of late-onset RN that recapitulates all of the histological features of RN observed in patients [27–33]. This second-generation model involves hemispheric irradiation using the Leksell Gamma Knife® (GK) Perfexion™ (Elekta AB; Stockholm, Sweden; http://www.elekta.com/), a state-of-the-art unit designed for stereotactic irradiation of patients with benign and malignant brain tumors, with a typical radiation dose of 50 Gy at the 50% isodose line. The GK enables reproducible treatments of a small volume (1 cm^3 or less) with a precision of better than ±0.5 mm in stereotactic space. Unlike clinical radiotherapy, which seeks to avoid damage to normal brain tissue, the GK-based irradiation scheme was chosen specifically to produce late time-to-onset RN in mice in an "experimentally tractable" (i.e., experimentally convenient) timeframe, with primary injury limited to the single ipsilateral hemisphere. A comprehensive description of the model and its dependence on radiation dose and fractionation were recently published [30].

Our current mouse model provides an opportunity to directly monitor radiologic progression of RN at high temporal resolution. To this end, T2-weighted spin-echo images of irradiated mice, covering the same anatomic region of the brain and collected at 1, 4, 8, and 13 weeks following a single 50-Gy dose of radiation, are shown in Fig. 1. Hyperintense areas in these images, due to edema, correspond with regions of RN in the brain. MR images begin to show hyperintense regions at ~4 weeks post irradiation, and these regions expand significantly by 13 weeks, indicating late onset and rapid progression of radiation necrosis. As noted earlier, an essential component of the critical evaluation of any animal model of RN is correlation of findings with gold-standard histology. This GK-enabled model of RN generates late time-to-onset tissue injury that recapitulates the histologic features seen in patients with confirmed radiation necrosis [28,29,31,33], Fig. 2. Further, as discussed below, edema-driven MR image hyperintensity observed in the brains of GK-irradiated mice correlates reproducibly and consistently with the severity and extent of histologic features characteristic of RN.

1.4. Histology

Radiation necrosis is associated with a wide range ("gestalt") of histologic features and changes. These changes include microhemorrhages, edema, vascular changes (increased numbers of delicate telangiectatic vessels, fibrinoid vascular necrosis, hyalinization), development of foamy macrophages, infiltration of polymorphonuclear leukocytes, astrocytosis, and loss of tissue elements, ranging from neuronal loss to frank involvement of all tissue elements with microcavitation. Recently, we described a semi-quantitative histologic *scoring system* for evaluation of the extent and severity of tissue injury in our GK mouse model of RN, demonstrated

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