Brain Radionecrosis Outside the Target Volume after Proton Radiotherapy: Analyses of Multiparametric Imaging and Proton Biological Effectiveness

Running title: Advanced imaging and proton biological effectiveness analyses for radionecrosis

Julianna K. Bronk MD, PhD, 1 Ahmad Amer, 2 Swapnil Khose, MD, 2 David Flint, PhD, 3 Antony Adair, PhD, 3 Pablo Yepes, PhD, 3,4 David Grosshans, MD, PhD, 1 Jason Johnson, MD, 2 Caroline Chung, MD, Msc 1

1Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
2Department of Neuroradiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
3Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
4Department of Physics and Astronomy, Rice University, Houston, TX, USA

Corresponding author: Julianna K. Bronk, MD, PhD, jkedwards@mdanderson.org

Author Responsible for Statistical Analyses: Not applicable

Conflicts of interest/Competing interests: None

Funding: Supported in part by Cancer Center Support (Core) Grant P30 CA016672 from the national Cancer Institute, National Institutes of Health, to The University of Texas MD Anderson Cancer Center (PI: PW Pisters).

Data Availability Statement for this Work: Research data are stored in an institutional repository and will be shared upon request to the corresponding author
Acknowledgments: The authors would like to thank Christine Wogan from the Department of Radiation Oncology Research for reviewing the manuscript.

Abstract (300 words)

Purpose: We present the case of a 48-year-old man with recurrent WHO grade II meningioma in the left occipital region who underwent subtotal resection followed by postoperative proton therapy to residual disease and the resection cavity. 14-months after radiation treatment completion surveillance imaging revealed numerous ring-enhancing infratentorial lesions both within and outside the high-dose field of concern for viable tumor. Here, we describe the use of advanced imaging and proton biological effectiveness analyses to (1) enable the diagnosis of radionecrosis and (2) ascertain intrinsic physical factors contributing to the development of radionecrosis in this patient.

Methods and Materials: Multiparametric MRI and Monte Carlo predictions of linear energy transfer (LET) and variable relative biological effectiveness (RBE) dose were performed.

Results: Dosimetric analysis revealed 9/10 lesions were located outside of the clinical treatment volume and 6/10 lesions received a dose of <60 Gy-RBE to 95% of the volume; however, increased proton LET values were found in lesions that received lower radiation doses. Dynamic susceptibility contrast (DSC)-, dynamic contrast-enhanced (DCE)-, and arterial spin labeling (ASL)-perfusion MRI findings were consistent with radionecrosis. Subsequent follow-up imaging revealed no further progression, and the patient was disease-free when this report was written.

Conclusions: We describe a case of brain radionecrosis following proton beam radiation occurring outside of the high dose radiotherapy volume. On initial radiographic detection of these lesions, the distant relationship between their anatomic location with respect to the patient’s treatment history reduced the suspicion of radionecrosis. However, on closer examination of intrinsic physical variables, radionecrosis lesions were present in regions that received lower dose but higher LETs. While conventional multi-sequence MRI was inadequate to distinguish between radionecrosis and tumor
progression, characterization of tissue physiology allowed for the correct diagnosis, highlighting the utility of advanced brain tumor imaging in the follow-up setting.

Introduction

Meningiomas account for about one-third of adult primary brain tumors. Although most meningiomas are benign, their intracranial location and the corresponding risk of complications from therapy may cause life-threatening morbidity.\(^1\) Radiotherapy after surgical resection is often recommended to reduce the risk of local failure in patients with recurrent or higher-grade disease.\(^2\)

Radionecrosis is one of the most severe late effects of radiation therapy to the brain, causing significant morbidity in symptomatic patients.\(^3\) Reports of the incidence of radionecrosis among patients with meningioma vary considerably (0.1%–23%),\(^4,5\) and the onset can be delayed beyond the typical window of 6-18 months.\(^6^\) Identification of radionecrosis after treatment remains a diagnostic challenge for clinicians given the similarities in radiographic appearance of necrotic lesions and progressing tumor on conventional multisequence magnetic resonance imaging (MRI).\(^3\)

Proton radiotherapy (PRT) is under prospective investigation for the treatment of meningioma as it decreases radiation dose to normal tissues, potentially resulting in preservation of functional capabilities and decreased risk of radiation-related toxicities\(^9^\)–\(^11\)—considerations that are essential for patients with meningioma, who can anticipate longer survival than patients with other primary brain tumors.\(^12\) However, in PRT, relative biologic effectiveness (RBE) varies along the treatment beam, resulting in an increase in biologically effective dose and linear energy transfer (LET) deposition at the distal segments of the spread-out Bragg peak which is hypothesized to contribute to radionecrosis development\(^13,14\).

We present an unusual case of radionecrosis after PRT that presented as new contrast-enhancing lesions, many of which were outside the high-dose treatment volume. Given the significant concern over whether these lesions were new metastatic disease or recurrent meningioma, we used
multiparametric MRI and proton biological effectiveness analyses to ascertain intrinsic physical factors contributing to radionecrosis development.

Case Report

A 48-year-old white man presented with 4-weeks of progressive memory difficulty, visual decline, and headaches. His previous medical history was significant for benign meningioma of the left occipital region, for which he had undergone craniotomy and resection 13-years prior. On this encounter, MRI revealed a complex solid-cystic intracranial mass within the previous resection cavity involving the torcula with extension anteriorly along the falcotentorial junction (Fig 1). The patient underwent craniotomy and resection of the mass. Histopathological examination of the resected lesion revealed a solitary fibrous tumor with 4 mitoses/10 hpf. Immunostaining showed a mildly elevated Ki-67 labeling index at 10%. Tumor cells were positive for STAT6, CD34, and BCL2 and negative for EMA. These features classified the tumor as a WHO grade II, meningioma. There was no evidence of brain invasion. Postoperative MRI revealed residual nodular tumor along the posterior falx and extending into the right tentorium. Given the findings of recurrent WHO grade II meningioma with residual disease after resection, the patient underwent postoperative radiation therapy with passive-scatter PRT to a dose of 60Gy-RBE in 30 fractions. The surgical bed and residual tumor made up the GTV and a 0.5cm anatomically constrained margin was added for the CTV which included the cerebellar tentorium. A 0.3cm PTV margin was added with daily kV imaging for image guidance. He tolerated treatment well, with only fatigue and grade 1 dermatitis.

A follow-up brain MRI obtained at 14 months after completion of radiotherapy revealed stable treated disease. However, numerous new ring-enhancing lesions were present in the bilateral superior cerebellar hemispheres as well as enhancing nodules along the superior vermis (Fig 1). These areas raised concern for recurrent meningioma versus new intracranial primary or metastatic disease versus
postradiation imaging changes. Review by a multidisciplinary care team led to a recommendation for short-interval follow-up to include brain and spine MRI.

Four weeks later, conventional MRI redemonstrated well-defined regions of T2-hyperintensity and superficial enhancement along the superior cerebellar vermis; multiparametric MRI findings favored radionecrosis rather than tumor progression (Fig 1). Spine MRI showed no evidence of metastatic disease to the bone or leptomeninges.

Due to progressive symptoms of double vision, dizziness, and headaches, a 3-month period of dexamethasone was begun and improvement was noted. 2-years after diagnosis, a course of bevacizumab (7.5mg/kg every 2-weeks) was begun for progressive symptoms corresponding to increased lesion-associated edema noted on T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR). The symptoms and FLAIR signal improved; however bevacizumab was discontinued after 3-cycles due to imaging findings suggestive of acute ischemia. 10-months after bevacizumab discontinuation, the patient had worsening symptoms of headache, imbalance, and blurry vision. Treatment options considered included surgical resection, steroids, or reinitiation of bevacizumab. Given the patient’s medical comorbidies and large area of radionecrosis, surgical resection was not recommended. Due to the patient’s history of insulin dependent diabetes and poor tolerance of steroids in the past, he was restarted on a lower dose of bevacizumab (5mg/kg every 3-weeks) and continued for 6-cycles. He has remained off therapy for 8-months with no new areas of necrosis or imaging findings suggestive of progressive disease.

Discussion
Radionecrosis is thought to develop from collateral radiation exposure to normal brain tissue leading to glial cell and vascular injury and ultimately resulting in local ischemia, chronic inflammation, and death of surrounding parenchyma.15,16 Malignant brain tumors are supported by angiogenic vasculature, a
poorly functioning, chaotically organized, “leaky” vessel network that may be more susceptible to vascular injury caused by radiation exposures. The permeability of the blood-brain-barrier and chronic tumor-associated inflammation may also prime surrounding brain tissue to radiation injury. Thus, the diagnosis of radionecrosis is often supported by the anatomic location of the lesion, with lesions near the tumor site and within the radiation treatment volume more likely to be necrosis than tumor recurrence. Likewise, the primary risk factors associated with development of radionecrosis center around radiotherapy variables including volume, fraction size, and dose, with secondary risk factors of prior radiation exposure, disease histology, and use of systemic therapy. Medical management with corticosteroids or anti-angiogenic therapies such as bevacizumab used here is preferred initially for patients experiencing symptoms. Cases refractory to medical management may require surgical intervention.

For this patient, the anatomic location of new contrast-enhancing lesions on MRI did not fit the profile of radionecrosis. While the treated cavity was in the supratentorium and had no evidence of treatment-related changes, the new lesions were in the cerebellum. Radionecrosis risk in the cerebellum was unlikely to have been influenced by tumor-associated factors such as angiogenic vasculature or inflammation but more likely reflected radiotherapy variables as part of the cerebellum was included in the treatment field. However, several cerebellar radionecrosis lesions were outside the high-dose treatment volume, further complicating diagnosis based on conventional radiologic assessment and treatment history alone.

*Proton biological effectiveness: A player in radionecrosis induction?*

During radiation treatment planning, proton radiation dose is converted to the photon dose-equivalent based on a uniform RBE factor of 1.1. However, preclinical studies have demonstrated that the RBE of PRT increases with LET. For protons, high-LET particles with increased RBE are present
within the falloff region of the Bragg curve. Clinically, the distal edge of the proton beam typically lies beyond the tumor target and within normal tissue. In one retrospective study, the incidence and location of normal brain tissue damage after PRT were associated with regions of increased LET.\textsuperscript{23} Specifically, hyperintensity on post-treatment T2-FLAIR MRIs from pediatric patients who underwent postoperative PRT for ependymoma were dependent on LET and dose.\textsuperscript{23} Investigators have hypothesized that radionecrosis risk may also be greater in high-LET regions. However, another retrospective review of PRT plans found no evidence of increased LET within necrotic regions.\textsuperscript{24} That study was limited by small patient groups, and the investigators concluded that the contribution of LET to radionecrosis is probably confounded by variations in absolute radiation dose and in patients’ inherent sensitivity to radiation.

In this case, when radionecrosis lesions were contoured on MRI and co-registered to the treatment planning CT, 9/10 lesions located in the anterior cerebellum had no overlap with the clinical treatment volume (CTV) (Fig 2). Our analysis of the dose delivered to the area of the brain in which radionecrosis developed showed that 6/10 lesions received a dose of <60 Gy-RBE to 95% of the volume (D95). As for the potential contribution of LET, our Monte Carlo predictions\textsuperscript{25} revealed that dose and LET distribution in radionecrosis lesions followed an inverse linear trend (Fig 3). For example, a lesion that received the lowest D95 (13.5 Gy-RBE) received the highest LET (LET\textsubscript{95} of 7.8 keV/\(\mu\)m). By comparison, the CTV received a D95 of 62.5 Gy-RBE with a LET\textsubscript{95} of 2.5 keV/\(\mu\)m.

Clinical correlations between brain radionecrosis and dosimetric variables in radiation therapy are still being defined; the contributions of LET to charged particle radiation therapy also remain unclear. This single-patient analysis highlights the significance of accounting for high-LET regions of the beam during PRT planning to reduce the risk of necrosis in normal tissue. In clinical practice, beam arrangements that result in overlap of multiple high LET beam regions in critical structures including the brain stem, optic nerves and optic chiasm should be avoided. Furthermore, we support the use of
biological response modeling to comprehensively describe variable RBE at the treatment planning stage.\textsuperscript{25-27}

\textit{Digging deeper for a diagnosis: Role of advanced imaging in distinguishing tumor progression from radionecrosis}

Both the radiographic features and clinical course of radionecrosis overlap considerably with tumor progression, which poses diagnostic challenges for determining the most appropriate intervention.\textsuperscript{28} In many cases, progression of previously stable neurologic symptoms often prompts urgent intervention. Alternative imaging studies such as dual-phase fluorodeoxyglucose(FDG) or amino acid positron emission tomography(PET) imaging have shown promise in detecting tumor progression versus radiation treatment effects, but have not been routinely implemented in clinical practice.\textsuperscript{29} Obtaining a tissue biopsy remains the gold standard for a definitive diagnosis of radionecrosis; however, in most practical settings, the diagnosis is made using imaging features alone. A significant limitation to relying on imaging features is that tumor and necrosis can present simultaneously, as has been found in more than 70\% of cases in pathological confirmation studies.\textsuperscript{30}

Multiparametric MRI is used as a noninvasive alternative to tissue biopsy in diagnosing radionecrosis as it provides insight into tissue biology and metabolism. Information on the biophysical processes occurring in brain tissue aids in distinguishing between necrotic versus viable tumor tissue.\textsuperscript{17,31,32} A panel of perfusion parameters, including relative cerebral blood volume(rCBV), permeability(Ktrans), and cerebral blood flow(CBF) are acquired through measurements of dynamic susceptibility contrast(DSC), dynamic contrast-enhancement(DCE), and arterial spin labeling(ASL), respectively.\textsuperscript{32} Although high-grade proliferative tumors generally have increased rCBV values owing to their higher microvascular density and the presence of collateral vasculature, radionecrosis usually has lower rCBV values. Likewise, DCE, which assesses contrast leakage across the blood-brain-barrier, is used as a surrogate marker of permeability and is quantified by the volume transfer constant(Ktrans). Areas
of radionecrosis typically have lower Ktrans values than those of tumor progression. Unlike DSC and DCE, ASL does not depend on the intravenous administration of gadolinium-contrast but rather quantifies magnetically labeled blood which acts as an endogenous tracer in the measurement of CBF. Although CBF is another measure of perfusion, it is not affected by leakage effects in the blood-brain-barrier, making it more quantitatively accurate than DSC. Expected differences in perfusion parameter findings between tumor and necrotic brain tissue are summarized in Table 1.

The contrast-enhancing lesions identified on this patient’s follow-up MRI were indistinguishable from those of tumor progression, and perfusion analysis provided a comprehensive characterization of tissue physiology (Fig 1). On ASL, no elevation in CBF was seen near the areas of enhancement. Although mild increased permeability (DCE) was associated with enhancing areas, there was no elevation in CBV. On follow-up imaging at 3-months and 2-years after the initial diagnosis of radionecrosis, both the size and the number of lesions were stable. An overall decrease in contrast enhancement at that time supported the diagnosis of radionecrosis. Moreover, perfusion parameters and CBF remained low in areas with associated contrast enhancement; at 3-months after diagnosis, mean DSC was 203/115 (SD 42/47); Ktrans was not elevated; mean ASL was 34 (SD 7.5); and mean ASL in the cerebellum was 31 (SD 5.5).

Conclusions
Here, we present a case in which diagnosis of radionecrosis after PRT was challenging as several lesions were located outside the target treatment volume. Considerable resources were dedicated to confirming the diagnosis and the patient’s clinical course of waxing and waning symptoms led to significant decrease in quality of life and required multiple lines of medical therapy. Although PRT has the dosimetric advantage of reduced integral dose to organs at risk, the location of the high-LET region of the beam should be considered during treatment design. Indeed, LET-optimized planning should be
explored in this context to maximize the therapeutic window when choosing PRT over other radiation modalities. Multiparametric MRI, particularly perfusion parameters, and use of multimodal imaging, such as PET, allow for noninvasive detection of radiation-induced damage with more accuracy than conventional MRI. This case highlights the need to better understand the induction, incidence, and severity of radionecrosis to facilitate strategies for improved prevention and diagnosis.

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
10. A Trial of Increased Dose Intensity Modulated Proton Therapy (IMPT) for High-Grade Meningiomas. In: https://ClinicalTrials.gov/show/NCT02693990.


Figure Legends

Fig 1  Narrative of the clinical course and correlates of advanced brain tumor imaging. Multiparametric MRI (mpMRI) was used before treatment, at the time of diagnosis of radionecrosis (RN), and at 3 months and 2 years of follow-up. Preoperative imaging showed a complex solid and cystic intracranial mass, with the cystic component measuring 6.5 cm×2.7 cm×2.7 cm in the anteroposterior, transverse, and craniocaudal planes and the solid nodular enhancing component measuring 2.9 cm×2.3 cm×3.2 cm. When radionecrosis was diagnosed, T1+contrast and T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) images revealed contrast-enhancing lesions in the cerebellum with mild edema that were indistinguishable from active disease. Permeability (Ktrans) and relative cerebral blood flow (rCBV) mapping at the level of the contrast-enhancing lesions were normal, supporting a diagnosis of radionecrosis. On follow-up surveillance imaging, the patient was noted to have a waxing and waning pattern of neurologic symptoms requiring medical intervention with steroids and bevacizumab therapy.
Fig 2  Necrosis lesions contoured on diagnostic MRI (right) and fused with the original planning CT scan (left). The location of the lesions with respect to clinical treatment volume (CTV; cyan line) and dose gradient delivered are shown at several levels.
Fig 3  (A) Radiation dose (Gy) versus linear energy transfer (LET) (keV/μm) for 10 identified radionecrosis lesions (black dots) and clinical treatment volume (CTV; in red). (B) D95 for fixed-relative biological effective (RBE) dose, variable RBE-weighted dose, Δ(D95 variable RBE weighted–fixed RBE), and LET95 are shown in tabular format at right.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>D95 fixed RBE (Gy)</th>
<th>D95 variable RBE weighted (Gy)</th>
<th>Δ(D95 variable RBE weighted–fixed RBE)</th>
<th>LET95 (keV/μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.5</td>
<td>25.9</td>
<td>12.4</td>
<td>7.8</td>
</tr>
<tr>
<td>2</td>
<td>33.6</td>
<td>48.7</td>
<td>15.1</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>44.5</td>
<td>61</td>
<td>16.5</td>
<td>4.7</td>
</tr>
<tr>
<td>4</td>
<td>46.5</td>
<td>62.7</td>
<td>16.2</td>
<td>3.75</td>
</tr>
<tr>
<td>5</td>
<td>52.3</td>
<td>59.8</td>
<td>7.3</td>
<td>4.5</td>
</tr>
<tr>
<td>6</td>
<td>53.75</td>
<td>65.7</td>
<td>11.95</td>
<td>4.5</td>
</tr>
<tr>
<td>7</td>
<td>60.5</td>
<td>62</td>
<td>1.5</td>
<td>3.2</td>
</tr>
<tr>
<td>8</td>
<td>60.5</td>
<td>66.7</td>
<td>6.2</td>
<td>3.4</td>
</tr>
<tr>
<td>9</td>
<td>60.9</td>
<td>66.5</td>
<td>5.6</td>
<td>3.5</td>
</tr>
<tr>
<td>CTV</td>
<td>61.6</td>
<td>60.9</td>
<td>-0.7</td>
<td>2.5</td>
</tr>
<tr>
<td>10</td>
<td>61.8</td>
<td>61</td>
<td>-0.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>
Table 1. Distinction between perfusion parameters for tumor versus necrosis

<table>
<thead>
<tr>
<th>Perfusion parameter</th>
<th>Measurement</th>
<th>Metabolically active tumor</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral blood volume (rCBV)</td>
<td>Dynamic susceptibility contrast (DSC)</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Permeability</td>
<td>Dynamic contrast-enhancement (DCE)/Ktrans</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Cerebral blood flow (CBF)</td>
<td>Arterial spin labeling (ASL)</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>