Radiation necrosis following treatment of high grade glioma—a review of the literature and current understanding

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Abstract Radiation therapy is an integral part of the standard treatment paradigm for malignant gliomas, with proven efficacy in randomized control trials. Radiation treatment is not without risk however, and radiation injury occurs in a certain proportion of patients. Difficulties in differentiating recurrence from radiation injury complicate the treatment course and can compromise care. These complexities are compounded by the recent distinction of two types of radiation injury: pseudoprogression and radiation necrosis, which are likely the result of radiation injury to the tumor and normal tissue, respectively. A thorough understanding of radiation-induced injury offers insights to guide further therapies. We detail the current knowledge of the mechanisms of radiation injury, along with potential targets for therapeutic intervention. Various diagnostic modalities are also described, in addition to the multiple options for treatment within the context of their pathophysiology and clinical efficacy. Radiation therapy is an integral part of the multidisciplinary management of gliomas, and the optimal diagnosis and management of radiation injury is paramount to improving patient outcomes.

Keywords Radiation necrosis · Radiobiology · Pseudoprogression · Radiation injury · Radiosurgery · Radiation

Introduction

The current standard treatment regimen for patients with high-grade gliomas, specifically glioblastoma, is a multimodal algorithm comprised of surgical resection followed by adjunctive radiation and chemotherapy. Prior to the European Organization for Research and Treatment of Cancer (EORTC) trial published by Stupp et al. in 2005, a number of studies suggested a possible benefit of chemoradiation for malignant glioma [65, 107, 113, 138, 139] compared with surgical resection alone. This trial was the first phase III randomized clinical trial to demonstrate a clear benefit in overall survival with the combination of temozolomide (TMZ) and radiation following surgical resection [122]. Accordingly, patients with newly diagnosed glioblastoma receive external beam radiation therapy (EBRT; 60 Gy in 30 fractions) with concomitant oral TMZ (75 mg/m² for 42 days), followed by maintenance TMZ (150–200 mg/m² in a 5/28 schedule) for six additional cycles.

Following the incorporation of adjunctive chemoradiation into the standard of care for glioblastoma, many studies have radiographically and histopathologically documented a rise in the number of treatment-related injuries: up to a threefold increase compared with radiation alone [11, 13, 14, 21, 31, 126]. Two distinct entities of radiation-induced injury have since been described: pseudoprogression and radiation necrosis. Pseudoprogression is characterized by early
enhancement, often occurring within 2–5 months from initiation of adjunctive therapies, with a self-limited course and eventual resolution both clinically and radiographically [13, 21, 31, 48, 140]. Conversely, radiation necrosis generally occurs from 3 months to more than a year after completion of chemoradiation, often demonstrating histologic findings consistent with necrosis (i.e., white matter and cell necrosis, endothelial apoptosis, increased vascular permeability, edema, and gliosis) without immediate resolution [3, 7, 70, 81, 82, 128, 150]. Although some have postulated a spectrum of radiation-induced injuries, ranging from pseudoprogression as a milder and earlier form of radiation necrosis, clinical and histologic evidence supports the notion of these processes as two distinct entities. Current data suggest that pseudoprogression may represent a combination of treatment effect on the residual tumor cells and breakdown of the blood-brain barrier (BBB), whereas radiation necrosis likely stems from radiation injury to the adjacent peritumoral white matter.

The presence of certain post-treatment radiographic findings, such as increased MRI T1 post-gadolinium contrast enhancement, implies a spectrum of possible diagnoses including pseudoprogression, radiation necrosis, and tumor progression. Such a differential, which may also include a mixed lesion, invariably complicates the treatment course. In the setting of tumor recurrence, the patient may require an alternative chemotherapeutic agent and possibly a re-operation. Conversely, radiation necrosis may be more effectively managed conservatively with steroids, although some cases may also require re-operation for symptom relief. Pseudoprogression can be managed conservatively with routine serial imaging. Consequently, the correct diagnosis becomes critical in guiding therapy and improving prognosis. We describe in this review the basic biology, radiographic diagnosis, and management of radiation necrosis.

**Biology of radiation injury**

Radiation therapy has been a standard treatment modality for a variety of intracranial pathologies, with its effectiveness limited by the potential for collateral injury to peritumoral tissue. Current understanding points to a dynamic and continuous response of the central nervous system (CNS) tissue to radiation, in which radiation therapy generates both immediate and delayed tissue damage [128, 143]. Acute injuries can result from radiation-induced endothelial cell apoptosis, which results in disruption of the BBB and consequent peritumoral tissue edema [70, 83]. Inflammatory cascades activated by radiation injury are exacerbated by the chronic hypoxia from endothelial remodeling, further promoting the microenvironmental changes that lead to radiation necrosis. Breakdown of the BBB may also enhance the effectiveness of chemotherapeutic agents, with the unintended consequence of contributing to injury of the peritumoral tissue.

The incidence of radiation necrosis is estimated at 3-24% in the setting of focal irradiation [13, 66, 76, 84, 106, 114, 118, 149] and may be threefold higher with concurrent chemotherapy [11, 21, 31]. The current paradigm, based primarily on radiographic and clinical observations, differentiates early (<2 months) post-treatment effects from later (>3 months) findings. The late radiographic findings most often occur 3–12 months following completion of chemoradiation, although delayed presentations are documented for up to 2 years post-treatment [43]. Several studies have alluded to a direct relationship between radiation-induced injury and different radiation doses, fractionation schemes, and adjuvant treatments [9, 68, 76, 77, 106]. A recent retrospective multivariate analysis of 426 patients by Ruben et al. [106] determined the most important risk factor to be total radiation dose, but also found an odds ratio of 5.8 to developing radiation necrosis with concomitant chemotheraphy administration. A number of key epigenetic and in vitro studies have highlighted the crucial role of O6-methylguanine–DNA methyltransferase (MGMT) promoter methylation in increasing TMZ sensitivity [10–12, 17, 20, 35, 40, 49, 50, 102].

Several epigenetic studies have previously demonstrated a strong correlation between MGMT gene promoter methylation and increased effectiveness of TMZ in the treatment of glioblastoma [10, 12, 17, 35, 40, 49, 50, 102]. MGMT is an enzyme that removes alkyl groups from the O6 position of guanine to prevent the accumulation of O6-methylguanine, thus inhibiting apoptosis [72, 89]. MGMT promoter methylation silences its expression, diminishing the cell’s capability to repair chemoradiation-induced DNA damage and resulting in cell death.

Histopathologic changes found in radiation necrosis include coagulative and liquefactive necrosis predominately in the white matter, with associated endothelial thickening, vascular hyalinization, fibrinoid deposition, and calcification [100, 105, 112, 134, 146, 150]. These findings are thought to lead to delayed injury, as a result of chronic microenvironmental changes secondary to vascular and parenchymal atrophy, fibrosis and necrosis [63, 150]. Mechanisms underlying this secondary injury include uncontrolled chronic inflammation, microvascular restructuring leading to hypoxia/ischemia and chronic oxidative stress, and inhibition of neurogenesis [1, 3, 7, 63, 81, 82, 128, 150]. The cells most vulnerable to radiation are oligodendrocytes, endothelial cells, and neural precursors. Apoptosis is the predominate mechanism of cell death, involving both p53-dependent and independent mechanisms [1, 94, 108, 143].

Animal models highlight the upregulation of pro-inflammatory transcription factors such as NF-κB, which
increase cytokine production within several hours of irradiation [25, 53, 63, 67, 99, 124, 147, 150]. One key upstream cytokine is tumor necrosis factor-α (TNF-α), which acts to upregulate other pro-inflammatory cytokines to increase BBB permeability, increase leukocyte adhesion, activate astrocytes, and induce endothelial apoptosis [3, 78, 142]. Treatment with anti-TNF antibodies obviates the radiation-induced astrogliosis, BBB damage, microvascular changes, and abscopal effects on adjacent brain tissue [3, 142]. An important downstream molecule is intercellular adhesion molecule-1 (ICAM-1): a transmembrane glycoprotein expressed on the surface of endothelial cells and the principal mediator of leukocyte-endothelial cell adhesion necessary for leukocyte diapedesis [34, 42, 80, 88, 93, 124, 142]. Radiation-induced leukocyte adhesion and BBB permeability are attenuated with anti-ICAM antibodies [148].

Glial cell versus vascular hypothesis

Histological findings of radiation necrosis consist primarily of demyelination and vascular abnormalities, eliciting two hypotheses for the principal cell-type leading to radiation necrosis: either glial or vascular involvement [63, 146]. In the glial hypothesis, oligodendrocytes have been implicated as the target cell because radiation injury is predominated by white matter necrosis and demyelination. Irradiation results in O-2A progenitor cell apoptosis within the rat CNS, and can contribute to astrogliosis by promoting terminal differentiation into type 2 astrocytes [135, 136]. Belka et al. [7] offer a detailed review of the activated cellular and molecular mechanisms.

The alternative vascular hypothesis posits that acute injury to the endothelial cells produces vascular abnormalities which result in an overall reduction blood vessel density [16, 73, 100]. Experimental evidence in rats by Lyubimova et al. [73] indicated a time-dependent progressive decline in endothelial cell density up to 52 weeks after irradiation, with about 50% of rats developing radiation necrosis. The resultant chronic ischemia produces a nutrient insufficiency and increases oxidative stress. This hypoxic environment leads to a substantial increase in reactive oxygen species (ROS) which initiate secondary injury cascades [6]. The oligodendrocytes and myelin are especially vulnerable to oxidative injury, which coincides with the findings of necrosis in white matter. However, the relative predilection of necrosis for white matter, as opposed to grey matter, is not completely clear. Gray matter contains neuronal cell bodies, which exhibit greater oxygen-dependency, indicating that multiple mechanisms are in effect. It is important to note that neuronal apoptosis and inhibition of neurogenesis does occur [75, 81, 82], and likely accounts for the widespread cognitive deficits reported in 20-50% of patients receiving whole-brain radiation therapy [30]. However, high-grade glioma patients only receive radiation to the volume of the contrast-enhancing lesion and surrounding edema plus a 2-cm margin; thus the proportion of patients with cognitive deficits in this patient population is presumed to be lower.

The pathway leading to radiation necrosis depends on the interaction between tumor cells, the vasculature, and the normal tissue within the irradiated area. Endothelial cell injury results in BBB breakdown, increased permeability, and increased radiographic enhancement as a consequence. In conjunction with other cellular processes, this injury likely provokes a chronic inflammatory state through the recruitment of leukocytes (e.g., via ICAM-1), which stimulate stress-induced molecular pathways and promote the delayed injury seen in radiation necrosis. Recent focus has been placed on the role of vascular endothelial growth factor (VEGF), which is increased in the setting of hypoxia and appears to play an important role in brain injury [87].

Pseudoprogression

Numerous reports describe a clinically insignificant process identified via serial post-treatment MRI [13, 21, 31, 48, 140]. The imaging in these patients displays T1 post-gadolinium enhancement of the resection cavity within 2 months of chemoradiation, which spontaneously resolves without additional treatment. The contrast enhancement and edema seen in pseudoprogression likely reflect the transient attenuation of the BBB, as opposed to the endothelial cell apoptosis and neuroinflammation seen in radiation necrosis [70, 83]. Histologic analysis of the enhancing tissue displays no evidence of tumor, characterizing this process as a pseudoprogression. With the increased use of serial post-operative radiographic imaging, pseudoprogression has been reported in 15-20% of patients undergoing concomitant chemoradiation in several case series [11, 21, 31, 41, 54]. This process is thought to correlate with treatment effect on tumor cells and not on peritumoral normal tissue. As such, many clinicians have advocated a period of cautious observation of up to 12 weeks following chemoradiation before the diagnosis of recurrence is considered [38, 145]. Brandes et al. [11] recently identified a significant correlation between MGMT methylation status and pseudoprogression, with 91% of MGMT methylated tumors demonstrating pseudoprogression.

Diagnosis of radiation necrosis

Conventional MRI cannot reliably differentiate tumor recurrence/progression from treatment effect [13, 66, 86, 149] (Fig. 1). Radiation necrosis, tumor recurrence, and pseudoprogression all cause destabilization of the BBB, resulting in
nonspecific T1-weighted post-gadolinium enhancement. Post-operative and post-treatment enhancement is therefore a non-specific marker of BBB breakdown, and can result from post-operative inflammation, seizures, tumor recurrence, or adjuvant treatment effects. Radiographic differentiation has dramatically improved with the integration of functional imaging to further evaluate tumor physiology and metabolism.

Conventional MRI

Several studies have described MR findings that may aid in the differentiation between recurrence and radiation necrosis. Kumar et al. [66] described such morphologic features of enhancement as Swiss cheese, soap bubble enhancement, remote or new to be more consistent with radiation necrosis. In addition, Mullins et al. [86] noted lesion multiplicity, corpus callosum invasion, and sub-ependymal spread to be correlated with tumor recurrence. Integrating these findings improves the diagnostic accuracy, but the limitations of diagnosis solely based on conventional MR findings are well documented [13, 61, 66, 86, 98, 103, 104, 109, 117, 149].

Macdonald et al. [74] previously published objective radiographic criteria based initially on contrast-enhanced computed tomography (CT), and later applied to MRI, to assess tumor response to adjunctive therapies. Macdonald and co-workers sought to define radiographic response based on enhancement, with a greater than 25% increase in enhancing lesion as a concern for progression. Since its adoption, the Macdonald criteria have served as an integral tool in standardizing clinical trials to date. Although the Macdonald criteria remain the most widely used instrument of standardization between clinical trials, several studies have pointed to its limitations and difficulty in application to multi-focal or irregular lesions, inclusion of the non-enhancing component, or measurements involving the cystic wall [52, 120, 133].

In 2010, the Response Assessment in Neuro-Oncology Working Group proposed new response criteria for clinical trials of high-grade gliomas [141]. Within the first 12 weeks of completing chemoradiation, progression is defined either
by new enhancement beyond the 80% isodose line or by histopathologic confirmation. Following 12 weeks, disease progression may be signified by: new enhancement despite corticosteroid use, greater than a 25% sum increase, an otherwise unattributed clinical deterioration, or an increase in MRI T2/fluid-attenuated inversion recovery (FLAIR) while on anti-angiogenic therapies. Future clinical trials are needed to correlate these recommendations with primary end points.

Diffusion imaging techniques

The magnitude and direction of free water movement are quantified with diffusion weighted imaging (DWI), by way of the apparent diffusion coefficient (ADC) for magnitude and diffusion tensor imaging (DTI) for direction. Tumor recurrence exhibits areas of high cellularity, which restrict water mobility. On the other hand, an increase in the ADC connotes increased water mobility, as seen in radiation necrosis. The sensitivity and specificity of DWI has yet to be fully characterized, but several small cohort studies have displayed promise in utilizing the ADC and ADC ratios (ratio of the ADC of the enhancing lesion compared with the non-enhancing ADC) in differentiating radiation necrosis from recurrence [5, 8, 51], but can be severely hindered and confounded by surrounding edema [18, 19]. Two other small studies have also pointed to the potential advantages of incorporating DTI into a diagnostic algorithm, although there may be limitations of its implementation [61, 125].

Magnetic resonance spectroscopy

The metabolic profile can be determined with proton MR spectroscopy and has been extensively studied as a tool to discriminate between radiation necrosis and recurrence [2, 36, 95, 104, 149]. Radiation necrosis has been shown to dramatically reduce N-acetyl aspartate (NAA) with variable changes to choline (Cho) and creatine (Cr) [26, 27, 97, 104, 110, 111, 125]. High Cho is correlated with disease progression, whereas low Cr is more consistent with radiation injury [27, 104, 111, 112]. Ando et al. [2] determined a 64% sensitivity and 83% specificity for a Cho/Cr threshold of 1.5 for the diagnosis of tumor recurrence. By increasing this threshold to 2, the sensitivity and specificity were further elevated to 87% and 89%, respectively [71]. Plotkin et al. [95] and Dowling et al. [36] found an 89% sensitivity and 83% specificity for tumor recurrence by combining thresholds of 1.17 for Cho/NAA and 1.11 for Cho/Cr. Smith et al. [116] developed a decision model using Cho/NAA with 85% sensitivity and <70% specificity. However, these studies are limited by their lack of histopathologic confirmation. Rock et al. [104] correlated histopathology with MR spectroscopy, demonstrating reliability with calculating Cho/NAA, NAA/Cr, and NAA/Cho ratios in the setting of pure lesions. In this regard, the study also highlighted the limitations in spatial resolution of less than 1 cm, especially with heterogeneous lesions consisting of both progressive tumor and radiation injury [104].

Perfusion imaging techniques

MR perfusion utilizes dynamic contrast enhancement to measure relative cerebral blood volume (rCBV) and determine the degree of vascularity and hemodynamics. Hyper-perfusion is seen with tumor recurrence [4, 29] and occurs as a consequence of increased metabolic activity and neo-angiogenesis resulting from increased VEGF expression [57]. Conversely, radiation necrosis consists mainly of ischemia-related changes caused by occlusive vasculopathy [39]. A prospective study of 20 patients by Sugahara et al. [123] indicated an rCBV of <0.6 or >2.6 to suggest radiation necrosis or tumor recurrence, respectively. A major caveat is in the setting of a rapidly growing tumor, which can exceed its blood supply and result in necrosis or states of hypoperfusion. Other limitations include limited availability, mixed tumor/necrosis lesions, and pseudoresponse from anti-angiogenic therapies [56, 58]. Although perfusion imaging shows promise, additional detailed studies are needed before its inclusion as a diagnostic modality.

Positron emission tomography (PET)

PET imaging utilizing various tracers has provided mixed results in identifying true tumor recurrence [22, 121, 130]. Initial studies of fluorine-18 fluorodeoxyglucose ($^{18}$F-FDG) PET reported a sensitivity and specificity within 80-100% [33, 37, 45, 62, 90, 132], but lacked histopathological correlations. More recent studies [46, 60, 92, 101, 121] have reported a sensitivity and specificity as low as 40% and 22%, respectively, in differentiating recurrence from necrosis—owing largely to the myriad of non-neoplastic pathologies that can cause elevated glucose metabolism (e.g., non-specific inflammation).

A number of molecular tracers have also been tested. $^{11}$C-Methionine, an amino acid tracer, has been the most extensively evaluated, with studies reporting sensitivities and specificities of 75-100% and 60-75%, respectively [32, 119, 127, 130, 131, 137]. $^{11}$C-Methionine was also demonstrated to be superior to FDG-PET [137]; however, the greatest limitation is the short half-life, which necessitates an on-site cyclotron [131]. Other amino acid tracers include 3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine ($^{18}$F-FDOPA) [24] and O-(2-$^{18}$F-fluoroethyl)-L-tyrosine ($^{18}$F-FET) [79, 96, 98] and display promising initial results. In addition, the tracer 3′-deoxy-3′-$^{18}$F-fluorothymidine ($^{18}$F-FLT) is DNA-based and is a more specific marker of proliferation.
This tracer was reported in two small pilot studies to be a powerful predictor of tumor progression [23, 55].

Management of radiation necrosis

Medical treatment

Corticosteroids play a significant role in the medical management of radiation necrosis by counteracting the radiation-induced vascular endothelial damage that leads to BBB breakdown. Similarly, inflammatory cascades can also be suppressed with steroid administration. Steroid treatment can be titrated to benefit the clinical status of the patient and may be weaned off after a period of symptomatic exacerbation [115]. However, in some cases symptoms can return after steroid cessation, necessitating long-term steroid use. Steroid treatment must be discussed within the context of the risks associated with prolonged systemic administration resulting in immunosuppression, psychiatric disturbances, myopathy and sequelae of endocrinologic compromise: hypertension, diabetes mellitus, osteoporosis, weight changes, and thickening of facial subcutis.

Proposed pathophysiologic mechanisms of radiation necrosis also include vascular damage leading to microthrombosis. Some authors have investigated anticoagulation therapy for the treatment of radiation necrosis unresponsive to steroid therapy and have demonstrated limited success, in which treatment with heparin and warfarin leads to partial recovery of function in five of eight patients with cerebral radiation necrosis [44]. One patient experienced a recurrence of symptoms following discontinuation of anticoagulation therapy, which was reversed again by resuming anticoagulation treatment. However, this treatment strategy has not been validated in larger trials.

As described above, the regional hypoxia of radiated brain parenchyma, upregulation of hypoxia-inducible factor-1-alpha, and subsequent increases in vascular endothelial growth factor (VEGF) all likely play a role in increased vascular permeability, edema, and necrosis. Several case series have shown reductions in radiation necrosis with administration of bevacizumab, a monoclonal anti-VEGF antibody, in combination with standard therapies [47, 129, 144]. These reports have demonstrated an improvement in contrast-enhancing volumes and FLAIR MR sequences, along with a reduction in daily steroid requirements [47, 144]. A recently published pilot study also provided class I data supporting the benefits of bevacizumab in the treatment of symptomatic radiation necrosis [69].

Evidence suggests a dual role for bevacizumab: to act in synergy with chemoradiation but also protect against radiation necrosis [59, 69, 129]. Blocking VEGF may modulate unstable glioma-stimulated vascular membranes, which would attenuate both coagulative and liquefactive necrosis. However, further studies are needed to elucidate these mechanisms. In addition, post-treatment MR imaging displays a decrease in T1 post-gadolinium enhancement. The implications of this imaging finding require further investigation as there exists a disconnect between the radiographic findings and clinical outcomes.

Hyperbaric oxygen treatment (HBOT) is also employed with the goal of increasing parenchymal oxygen concentration in order to stimulate angiogenesis and restore the regional blood supply compromised by radiation-mediated vascular injury. HBOT treatment has been shown to be beneficial in pediatric patients with radiation necrosis [28], and in smaller series and case reports [15, 64]. One study of prophylactic HBOT after SRS for metastases demonstrated decreased rates of white matter injury without known benefit [91]. Because single institution studies vary widely due to patient selection bias, randomized trials will be required to delineate the true benefit, if any, of HBOT.

Surgical management

Surgical resection is generally indicated for cases of radiation necrosis which are symptomatic, medically intractable, and located in a region that is surgically accessible without incurring additional significant neurologic morbidity. Surgical resection reduces mass effect, edema and lowers intracranial pressure, resulting in lasting clinical improvement in the majority of patients [85]. Radiation necrosis can often be differentiated from tumor recurrence intra-operatively, appearing very firm, pasty and avascular in contrast to tumor, which is typically soft, purple and very vascular. Either lesion can be resected in piecemeal fashion with surgical microscissors or ultrasonic aspiration.

Conclusions

Radiation therapy is an efficacious, essential component of the treatment paradigm for malignant gliomas. Radiation therapy carries a risk of radiation-induced injury. This risk of radiation injury is further exacerbated with the concomitant use of chemotherapeutic agents, and complicates the accurate diagnosis paramount to optimizing patient outcomes.

Multiple radiological and nuclear medicine techniques are available to help differentiate between radiation necrosis and tumor progression. However, these anatomic and metabolic imaging techniques all have inherent limitations in sensitivity and specificity. Further refinement of these techniques, as well as a combination of modalities may increase diagnostic accuracy. Surgical biopsy can be used in cases of equivocal imaging.
Once diagnosed, radiation necrosis may be managed with many tools, ranging from observation to corticosteroid administration to surgical resection for refractory and symptomatic lesions. Further investigation is required to assess the efficacy of alternative treatments such as hyperbaric oxygen therapy or anti-VEGF therapy.

Conflicts of interest None.

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Acta Neurochir


Comment

This review is an important read for neurosurgeons involved not only in the care of high-grade gliomas, the main point of analysis in the paper, but those who deal with radiation therapy in general. Up-to-date understanding of the biochemical mechanisms of radio necrosis is essential to interpret clinical and radiological events that develop after such therapy. With the increased use of stereotactic radiosurgical techniques in management of neurological patients this review is highly topical.

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The authors provide an impeccable and timely review of the current understanding of (a) pseudoprogression and (b) radiation necrosis that have increased with chemoradiotherapy of grade III and IV gliomas as against (c) progression that will invariably take place:

a. Pseudoprogression is early enhancement and expansion around the resection cavity seen at two to five months that will resolve in a few months. It does not require surgery - but without previous experience it may be hard to believe in the wait-and-see policy. In glioblastomas, ultraearly progression in spite of radiotherapy is a possibility but in our hands much less frequent than pseudoprogression.

b. Radiation necrosis may appear at some six months to over a year after chemoradiotherapy. A somewhat open question is whether BCNU wafers piled in the resection cavity increase the risk of radionecrosis. A question ages old is whether and how to differentiate radiation necrosis from glioma progression by various MRI sequences or PET - I find that problem somewhat academic as by definition there is always progressing glioma tissue in the area that looks like radiation necrosis. More important than a strict imaging-based distinction between the two is - in my mind - that we are prepared to re-resect lesions that produce significant brain edema. The bottom line is that radiation necrosis often requires prolonged corticosteroid therapy to alleviate symptoms from vasogenic brain edema - with a long list of side effects of corticosteroids as the price to pay.

WE MUST FIND OUT SOMETHING LESS NASTY THAN CORTICOSTEROIDS TO ALLEViate VASOGEnIC BRAIN EDEMA CAUSED BY GRADE III-IV GLIOMAS OR RADIAtion NECROSIS.