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Cerebral Radiation Necrosis: Incidence, Pathogenesis, Diagnostic Challenges, and Future Opportunities

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Abstract

Purpose of Review Cerebral radiation necrosis (CRN) is a major dose-limiting adverse event of radiotherapy. The incidence rate of RN varies with the radiotherapy modality, total dose, dose fractionation, and the nature of the lesion being targeted. In addition to these known and controllable features, there is a stochastic component to the occurrence of CRN—the genetic profile of the host or the lesion and their role in the development of CRN.

Recent Findings Recent studies provide some insight into the genetic mechanisms underlying radiation-induced brain injury. In addition to these incompletely understood host factors, the diagnostic criteria for CRN using structural and functional imaging are also not clear, though multiple structural and functional imaging modalities exist, a combination of which may prove to be the ideal diagnostic imaging approach. As the utilization of novel molecular therapies and immunotherapy increases, the incidence of CRN is expected to increase and its diagnosis will become more challenging. Tissue biopsies can be insensitive and suffer from sampling biases and procedural risks. Liquid biopsies represent a promising, accurate, and non-invasive diagnostic strategy, though this modality is currently in its infancy.

Summary A better understanding of the pathogenesis of CRN will expand and optimize the diagnosis and management of CRN by better utilizing existing treatment options including bevacizumab, pentoxifylline, hyperbaric oxygen therapy, and laser interstitial thermal therapy.

Keywords Radiotherapy · Radiation necrosis · Brain tumors · Gliomas · Stereotactic radiosurgery · Laser interstitial thermal therapy · Tumor progression · Imaging · Pseudo-progression · Bevacizumab · Biomarkers

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Introduction

Radiotherapy (RT) has been used to treat intracranial tumors for over half a century. Early RT modalities irradiated the whole brain, initially with kilovoltage, and later with megavoltage X-rays. In the late 1970s and early 1980s, the development of stereotactic radiosurgery (SRS), computed tomography (CT), and magnetic resonance imaging (MRI) enabled a more targeted approach to RT [1]. The earliest pathological evidence of radiation-induced brain injury was reported in 1930 in a 45-year-old man who received X-ray irradiation to the scalp [2]. In the 1980s, RT-related adverse events were characterized further by Sheline et al. into three distinct categories based primarily on their time of onset from RT, namely acute reactions which occur during the course of RT, early delayed reactions which occur few months to few weeks after RT, and late delayed reactions which occur several months to years following RT [3]. This characterization is utilized to this day. Multiple dose escalation RT trials found

cerebral radiation necrosis and the resultant edema to be a significant limiting factor despite observance of improved survival [1].

Cerebral radiation necrosis has been defined as a severe local tissue reaction that occurs at least 3–12 months after completion of RT, though it has been reported to occur several years after treatment completion. In this review, we aim to summarize the incidence, pathogenesis, genetics of RN, diagnosis strategies, judicious management outlining the currently available treatment options, and new challenges in the face of cerebral radiation necrosis.

Incidence

The incidence of cerebral radiation necrosis is influenced by multiple factors, including RT modality, total dose, dose fractionation, intracranial pathology, and diagnostic imaging modality used. Earlier studies evaluating conventional RT modalities documented a cerebral radiation necrosis incidence rate of 14–15% [4]. Newer RT modalities such as intensity-modulated RT (IMRT), image-guided RT (IGRT), interstitial RT (brachytherapy), and stereotactic radiosurgery (SRS) have minimized the risk of necrosis by decreasing the radiation injury to normal tissue. Nonetheless, the utility of SRS is majorly limited by cerebral radiation necrosis, since administering large doses in single fractions is expected to yield a significant necrotic burden, which sometimes may necessitate a craniotomy. With brachytherapy, the reported cerebral radiation necrosis rate is between 25 and 50% [4]. One can argue that the severity of and the necrotic burden may be higher with brachytherapy, with one study reporting that nearly 50% of their patients required a craniotomy due to clinical deterioration, increasing steroid dependency, or mass effect at the site of implantation [5].

Biopsy of the necrotic lesion is the gold standard for diagnosis cerebral radiation necrosis but is costly, invasive, and biased by sampling error. Furthermore, underestimation or overestimation of cerebral radiation necrosis also impacts the reporting of tumor response and local control rate, which in turn can skew findings of clinical trials.

CRN: Gliomas, Metastases, and Arteriovenous Malformations

RCTs by the Radiation Therapy Oncology Group (RTOG) demonstrated a higher incidence of cerebral radiation necrosis with high-dose RT (total radiation dose of ≥ 64.8 Gy) administered in 36 fractions among patients with low-grade glioma (LGG), and 54 fractions in patients with high-grade glioma (HGG), compared with low-dose RT, highlighting the dominant role of total radiation dose on the development of this pathological process [6, 7]. A meta-analysis of 29 studies on the utility of SRS in newly diagnosed HGG patients found the pooled cerebral radiation necrosis rate to be 6.5 (95% CI 0–33%) [8]. Concurrent bevacizumab therapy with SRS does not seem to increase the risk of cerebral radiation necrosis, though the current body of evidence addressing this question is limited [9].

In recent years, it has become evident that tumor biology and genetics play a role in radiosensitivity and consequently, cerebral radiation necrosis. In patients with metastatic brain tumors, retrospective studies report a cerebral radiation necrosis rate of 4.7–9.2% with SRS, at RT doses ranging from 18 to 30 Gy, with higher necrosis rates reported in studies utilizing higher RT doses [10–13]. For larger lesions (> 2–3 cm in diameter), the cerebral radiation necrosis rate has been reported to be 2.9–22.6% with RT doses of 8–35 Gy [12, 14, 15]. A higher cerebral radiation necrosis rate has been reported with postoperative SRS administered in a single dose compared to pre-operative SRS or SRS alone in a multicenter study [15]. Multifractionated SRS not only leads to lower cerebral radiation necrosis rates but has been shown to achieve higher local disease control rate compared with single-fraction SRS [16]. With symptomatic lesions necessitating biopsy, a majority reveal cerebral radiation necrosis rather than recurrent metastatic disease [17]. Concurrent systemic therapies and SRS reportedly lead to a cerebral radiation necrosis rate of 8% [18]. With concurrent immune-checkpoint inhibitor therapy and SRS, a meta-analysis found the pooled incidence of cerebral radiation necrosis to be 5.3% among patients with metastatic brain tumors [19].

Irradiation of arteriovenous malformations (AVMs) provides a unique opportunity to study radiation biology as these patients live a long time, there is very little solid tissue that is irradiated, and the majority of the effects relate to irradiation of the margin of cerebral tissue around the AVM. The fraction of brain volume that receives > 10 Gy is associated with an increased incidence of cerebral radiation necrosis. AVM studies also reveal heterogeneity in the incidence of cerebral radiation necrosis depending on location in the brain [20]. The actuarial risk of developing neuroradiological changes has been reported to be 31–32% [21, 22].

Pathophysiology

Cerebral radiation necrosis begins with radiation-induced vascular insult, which occurs within the first 24 h after radiation, and is followed by brain parenchymal injury [23]. Ionizing radiation produces reactive oxygen species in tumor cells, which lead to single- and double-stranded DNA damage. DNA repair pathways are subsequently activated, leading to cell cycle arrest and apoptosis of cells with irreversibly damaged DNA [4]. Endothelial cells are also damaged by radiation interacting with the plasma membrane which causes a

ceramide-induced apoptosis [24]. This initiates a cascade of events leading to cellular swelling and necrosis, production of more reactive oxygen species, and subsequent propagation of an inflammatory response involving cytokines and chemokines. This leads to the formation of fibrin-platelet thrombi and fibrinoid necrosis. Consequently, BBB disruption occurs and leads to cerebral edema [25, 26] (Fig. 1).

In addition to endothelial injury, radiation damages astrocytes, oligodendrocytes, and neural progenitor cells [27, 28]. The resultant inflammatory response and formation of necrotic tumor debris which is not readily removed aggravate the capillary permeability defects and promote demyelination. These changes characterize the early delayed phase of cerebral radiation necrosis, which may be difficult to distinguish from tumor progression [23]. The irreversible delayed phase of cerebral radiation necrosis has a spectrum of characteristics, ranging from focal radionecrosis to diffuse leukoencephalopathy with cerebral atrophy. Radiation-induced cerebral injury is predominantly seen in white matter [23].

The role of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 alpha (HIF-1α) in the pathogenesis of cerebral radiation necrosis has become more apparent in recent years. HIF-1α is a transactivator of VEGF, and its upregulation causes augmentation of VEGF production by astrocytes, which leads to angiogenesis [29]. However, vessels that originate from such a reaction are fragile and leak, causing perilesional edema which characterizes the acute phase of cerebral radiation necrosis. An increase in VEGF has been found in the perinecrotic area of necrotic cerebral foci in animal

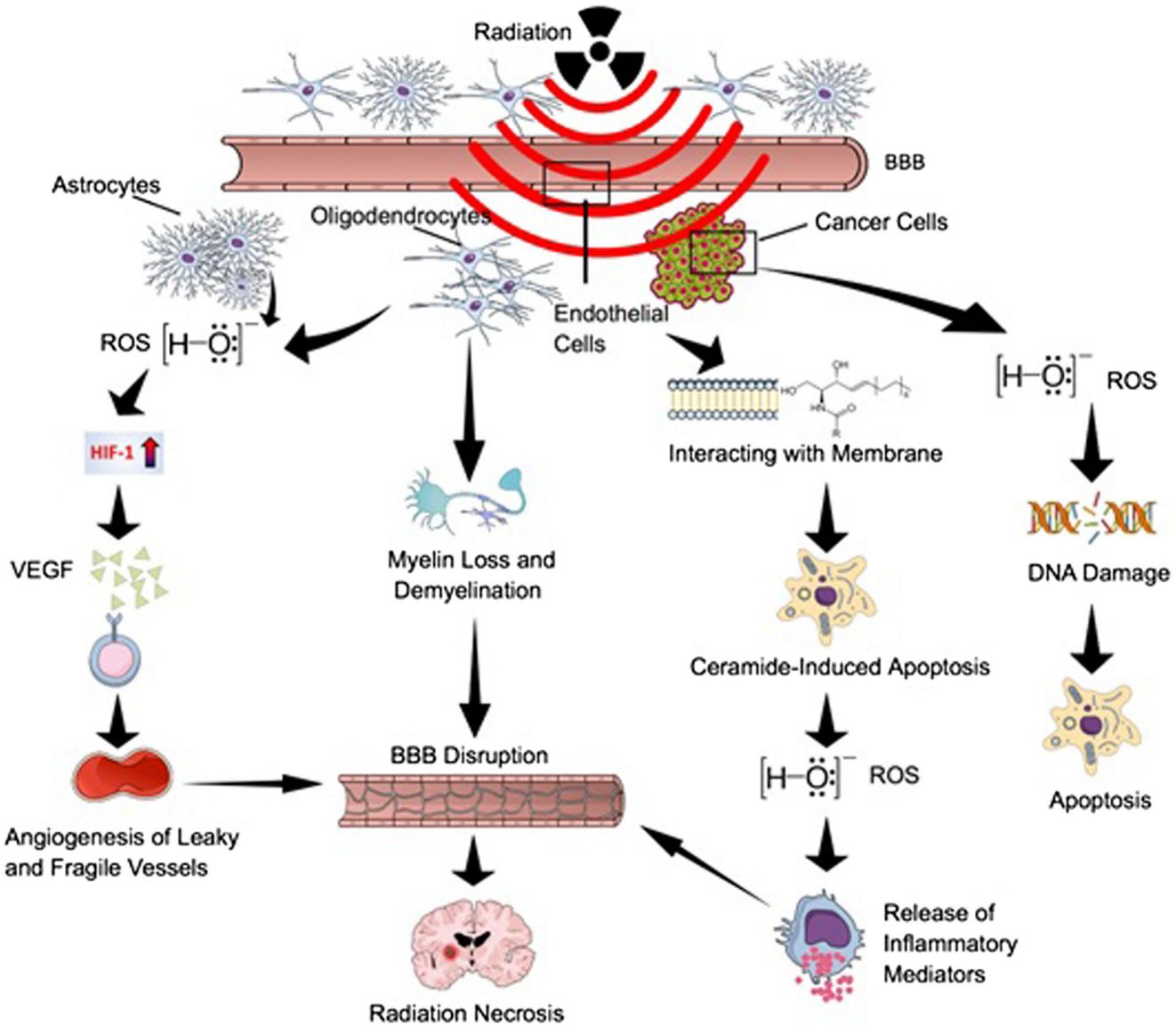


Fig. 1 An overview of the pathophysiology of radiation necrosis. ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; HIF-1, hypoxia inducible factor-1α; BBB, blood-brain barrier

models [30]. HIF-1α is also an important regulator of important chemokine axis mediators CXCL12-CXCR4, whose inhibition along with HIF-1α inhibition has been shown to mitigate the development of cerebral radiation necrosis in an animal models [31].

Histopathologic Characteristics

Histologically, cerebral radiation necrosis is characterized by the presence of geographical eosinophilic necrosis accompanied by gemistocyitic astrocytes representing gliosis with atypia. Additionally, fibrinoid vascular necrosis associated with dystrophic calcification, perivascular lymphoplasmacytic infiltrates and telangiectasias representing reactive vascular changes are also seen, though this finding is not very specific to cerebral radiation necrosis (Fig. 2) [32, 33]. Presence of pleomorphic and well-differentiated astrocytes within necrosis lesions in paucity is not uncommon and does not indicate tumor progression. Conversely, the presence of mitotically active tumor cells in predominance characterizes tumor progression. Often the histologic features of cerebral radiation necrosis and tumor progression coexist among surgically resected specimens, with a predominance of one set of features which entails a diagnosis (either cerebral radiation necrosis or tumor progression). A major limitation to current practice in gliomas is the lack of histopathological criteria for pseudoprogression, as opposed to true tumor progression. Although the presence of cerebral radiation necrosis on stereotactic biopsies in patients with malignant astrocytoma may be associated with improved survival compared to biopsies that reveal tumor progression [34], studies validating these findings are limited with contradictory results and further studies incorporating details of the molecular characteristics of tumors are needed [32, 33, 35].

Symptomatology and Risk Factors

Both tumor progression and cerebral radiation necrosis have similar symptomatology; however, the management of these entities is completely different. The symptomatology of cerebral radiation necrosis is generally subtle but depends on the location and size of the lesion(s); patients may present with cognitive deficits which are clinically obvious or, on the contrary, may be mild and require comprehensive neuropsychological evaluation to be identified [36]. In cases with larger lesions, cerebral edema could cause symptoms of raised intracranial pressure, which in severe cases can lead to fatal herniation [37]. Rarely, cerebral radiation necrosis may present with cerebral hemorrhage or breakthrough seizures [38].

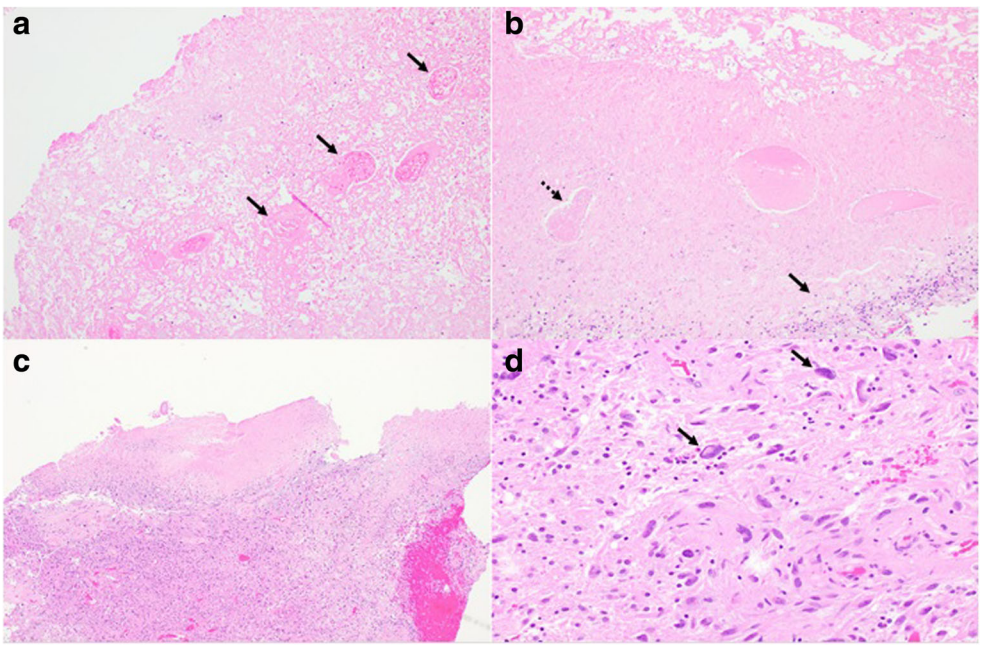


Fig. 2 **a** H&E stained section from brain tissue obtained from a patient with history of metastatic carcinoma that was treated with radiation. The tissue shows extensive necrosis, including necrosis of blood vessels (black arrow). No metastatic carcinoma was identified in the tissue sections. **b** H&E stained section from brain tissue obtained from a patient with history of glioblastoma that underwent surgical resection and radiation therapy. The tissue shows histologic features of RN, including necrotic brain parenchyma with necrosis of blood vessels (dashed arrow). There is a cluster of macrophages (black arrow) at the edge of the section. Areas with residual glioblastoma (**c**) were identified with bizarre pleomorphic cells showing treatment-related changes (arrows) (**d**)

Treatment-Associated Risk Factors

The cumulative radiation dose, fractionation size and schedule, treatment duration, volume treated, previous cranial irradiation, and the use of concurrent or adjuvant chemotherapy are all factors that play a role in the development of cerebral radiation necrosis [4]. Lesions > 1 cm in diameter are at the greatest risk of cerebral radiation necrosis. A radiation dose threshold of 50 Gy in 25 fractions has been established, below which the risk of cerebral radiation necrosis is thought to be minimal [39]. A greater than 5% risk has been associated at a cumulative dose of 72 Gy, fractionated at 2 Gy [40]. However, with re-irradiation, a cumulative dose of > 100 Gy has been reported to be the threshold beyond which cerebral radiation necrosis occurs [41]. Hypofractionation has been reported to be a safe and tolerable strategy for the treatment of recurrent high-grade gliomas without inferring an increased risk of cerebral radiation necrosis [42]. With SRS, the risk of cerebral radiation necrosis has a dose-response relationship, with a dose of 10 Gy to > 10.5 mL volume inferring a 35% risk of necrosis [40, 43]. This risk escalates to up to 50% with a 12 Gy dose to > 10-mL surface area [44]. Escalating fraction size has also been shown to increase risk, as was reported in one study in which 60-Gy dose was given in 35 vs. 30 fractions [45]. A dose-escalation study reported a 5% incidence of cerebral radiation necrosis 6 months post-RT, increasing to 8%, 9%, and 11% at 12, 18, and 24 months, respectively [40]. With cerebral re-irradiation, no correlation between the time elapsed from initial RT and re-irradiation and incidence of radiation necrosis was found upon a systematic review and analysis of the literature [41]. In terms of volume of dose received by volume of brain in cubic centimeter, RT dose ranging from 44.5–87.8 Gy has been reported to be statistically significantly associated with the development of cerebral radiation necrosis [46].

The additive effect of previous neoadjuvant therapies should also be considered. The use of BRAF inhibitors (BRAFi) concurrently with SRS found a 22% incidence of cerebral radiation necrosis in patients receiving BRAFi with SRS compared to 11% in patients that received SRS alone [47]. A study of melanoma patients receiving an immune checkpoint inhibitor (ICPI) and SRS for brain metastases also found a higher incidence of cerebral radiation necrosis, along with longer overall survival compared to patients who did not receive ICPI [48]. A second study found that in patients who underwent Gamma Knife radiosurgery, administration of ICPI was associated with a higher rate of cerebral radiation necrosis compared to patients undergoing chemotherapy and targeted therapy. As the use of immunotherapies and other targeted therapies increases, the rate of cerebral radiation necrosis may change compared with rates reported in the chemotherapy era [49]. We recently demonstrated the safety of Gamma Knife SRS in combination with bevacizumab for focally recurrent GBM; no radiation-associated adverse events were reported in our sample of 45 patients treated with a median margin dose and target volume of 17.0 Gy (range 13–24 Gy) and 2.2 cm^3 (range 0.1–25.2 cm^3), respectively [42]. Further studies however are still needed to assess the safety of Gamma Knife SRS and bevacizumab for the treatment of recurrent GBM.

Tumor-Associated Risk Factors

The risk of developing cerebral radiation necrosis varies with tumor location, histology, and genotype. An analysis of 5747 lesions, 15% of which were lesions of cerebral radiation necrosis based on radiographic evidence, revealed a statistically significant association between cerebral radiation necrosis and metastatic lesions of renal and non-small cell lung adenocarcinomas [50•]. HER2-amplification, BRAF V600+ mutational status, and ALK rearrangement all appear to be significantly associated with cerebral radiation necrosis. This study represents the first body of evidence on the association between tumor biology and cerebral radiation necrosis and has the potential for clinical implications. Nonetheless, in vivo studies on the genetic basis of cerebral radiation necrosis are scarce.

O6–methylguanine–DNA methyltransferase (MGMT) is an enzyme that removes alkyl groups from the O6 position of guanine and inhibits apoptosis. The methylation of MGMT promoter sequence silences its expression, which eventually results in cell death. While methylation of the MGMT promoter and mutations of isocitrate dehydrogenase 1 (IDH1) has been shown to predict pseudoprogression (PsP) in patients with GBM [51, 52], the role of these and other tumor-related factors in the development of cerebral radiation necrosis has not been thoroughly evaluated.

Individual Risk Factors

There is significant interpatient variability in radiosensitivity. Initial evidence to support a genetic basis for radiation toxicity stemmed from studying breast cancer patients, in whom about 90% of the variation in the development of radiation-induced telangiectasia was attributed to underlying genetic differences. Relatives of breast cancer patients with enhanced chromosomal radiosensitivity had also been reported to have higher radiosensitivity compared with relatives of individuals who do not project enhanced radiosensitivity [53]. Patients with ataxia telangiectasia, Fanconi anemia, and Bloom syndrome, all inheritable disorders of DNA damage surveillance and repair genes [54–56], all have a higher degree of radiosensitivity. The diverse genetic abnormalities responsible for these disorders suggest that radiosensitivity is a polygenic

trait involving multiple pathways, some of which are inheritable. Multiple approaches to identify a genetic basis have been employed, ranging from a candidate gene approach to identification of SNPs, all of which identify pieces of the puzzle, but fail to create a framework that could be implicated in radiosensitivity and radiation injury. In recent years, a broader genome-wide approach has been used to identify SNPs which are mapped to identify associations among a network of SNPs and a phenotype such as radiation injury.

A recent genome-wide association study found the varying risk of cerebral radiation necrosis of the temporal lobe with different single-nucleotide polymorphisms (SNPs) in a glioblastoma cell line (U87) treated with X-rays and H_2O_2. The most significant risk was found with SNPs effecting *CEP*128, which maintains normal functional cilia and potentially play a protective role against radiation injury [57•]. Inducing an A > G alteration in a *CEP*128 promoter yielded a variant (rs17111237) which impaired its promoter activity, leading to a knockdown of *CEP*128. This led to higher apoptosis and cell death of the U87 cell line and was associated with risk of temporal lobe radiation injury (hazard ratio = 1.45, range 1.26–1.66). This is the first study to implicate a radiation injury susceptibility gene (*Cep*128) and provides novel insight into the underlying mechanisms of radiation-induced brain injury.

Diagnostic Imaging, Cerebral Radiation Necrosis, and Tumor Progression

Several basic and advanced imaging techniques are available which can be utilized to distinguish tumor progression from cerebral radiation necrosis. MRI is the cornerstone modality for the imaging assessment of treatment response in brain tumors. The presence of enhancement has been widely accepted as a marker of tumor viability. However, the differential diagnosis for new post-treatment enhancing lesions is broad and includes all processes that alter the BBB permeability, including tumor progression, chemoradiotherapy-induced capillary damage, ischemia, and surgical trauma.

In the setting of cerebral radiation necrosis, the conventional MRI protocol often shows a ring-enhancing lesion in the treated tumor bed and edema in the surrounding area, a non-specific finding that can also be present in tumor progression [58]. The uncertainty in diagnosing cerebral radiation necrosis solely based on conventional radiological findings has been reported to be up to 15% [59]. With the growing use of immunotherapy, this uncertainty is expected to increase since immune response-related pseudoprogression tends to induce a similar contrast enhancement of lesions (Fig. 3) [59].

Multiple imaging features have been identified that favor a diagnosis of cerebral radiation necrosis [60]. These include the following:

- Enhancing focus post-radiation therapy at any time (indicating blood-brain barrier disruption)
- Enhancing focus at a distance from the original glioma site, within the radiation field limits with a biologically equivalent dose (BED) higher than 7410 cGy [61].
- New nodular enhancing lesion exhibiting soap bubble or Swiss cheese pattern
- Scalloped appearance of the enhancement (indicting diffuse white matter injury)
- White matter lesions greater in extent than gray matter lesions
- Overall greater FLAIR: enhancement volume ratio than compared with tumor progression
- High-signal lesions in the periventricular white matter on T2-weighted images

Lesion quotient (LQ) is the ratio of maximal nodular cross-sectional area (CSA) of a lesion as seen on T2WI, and the CSA of the enhancing lesion as seen on T1WI with contrast. An LQ of 0.3 or less has been reported in cases of pathologically confirmed cerebral radiation necrosis [62]. An LQ > 0.3 was found to be 80% sensitive and 96% specific for differentiation cerebral radiation necrosis from tumor progression, with a negative predictive value of 96%.

Advanced Brain Tumor Imaging

Advanced brain tumor imaging (ABTI) is a group of advanced MRI sequences and functional imaging techniques which allow the characterization of specific tissue phenotypic traits and help in differentiating between tumor cell proliferation and treatment-related changes. In addition to the standard-of-care MRI protocol, our institutional ABTI protocol includes diffusion-weighted imaging (DWI), susceptibility-weighted imaging, perfusion-weighted imaging (dynamic susceptibility contrast and pseudo-continuous arterial spin labeling), diffusor tensor imaging, and MR spectroscopy (MRS). Other advanced imaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can provide valuable functional information; however, they are not routinely used in the daily clinical practice.

Diffusion-weighted imaging (DWI) is an MRI technique that exploits the random Brownian motion of water molecules within a voxel to characterize normal and pathologic tissues. DWI enables measuring of diffusivity as an apparent diffusion coefficient (ADC), which can be used to help differentiate cerebral radiation necrosis from tumor

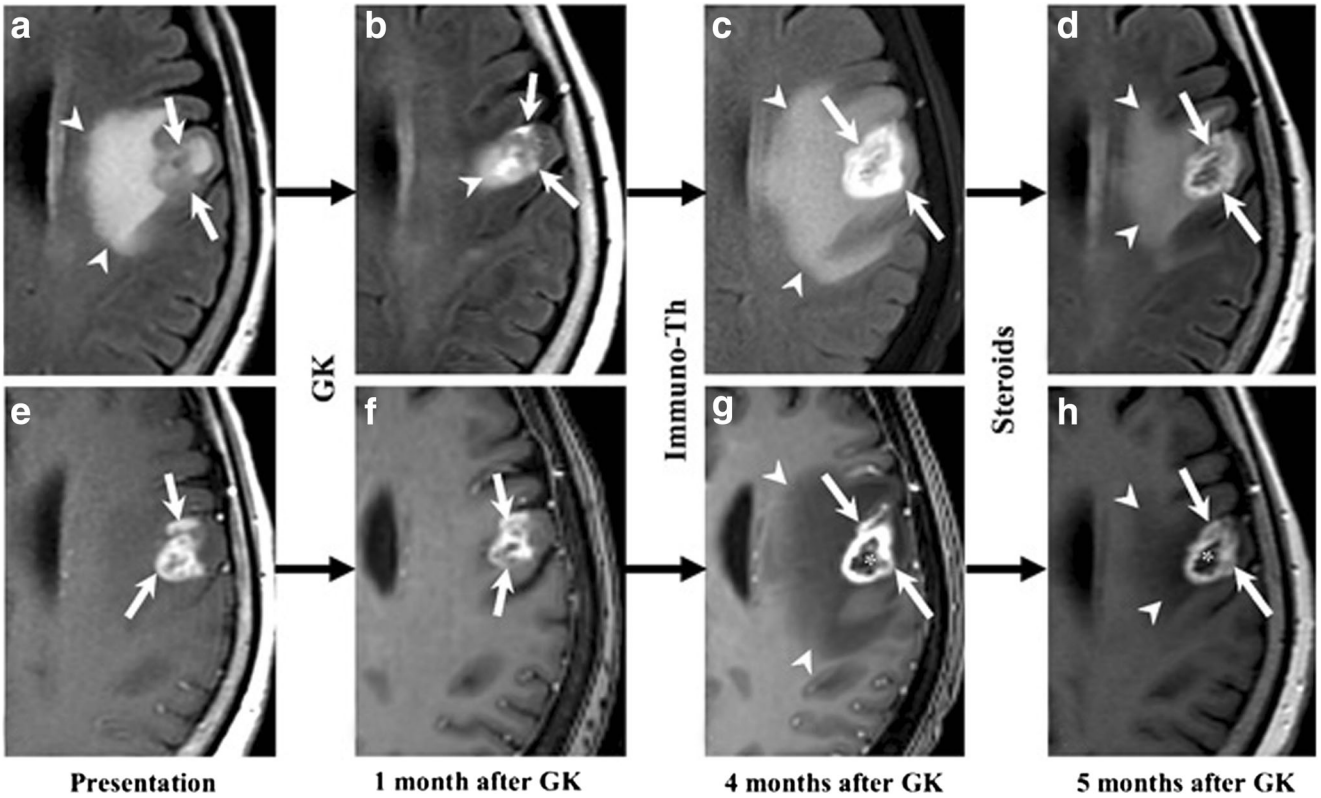


Fig. 3 Female patient in her sixth decade of life with a diagnosis of lung adenocarcinoma and sudden onset of seizures. Serial MRI of the brain with contrast with axial FLAIR (**a**–**d**), and axial post-contrast T1 (**e**–**h**) images. At the initial scan, an ill-defined, T2/FLAIR isointense (arrows in **a**), heterogeneously enhancing (arrows in **e**), cortico-subcortical nodule is seen in the left precentral gyrus with associated mass effect and vasogenic edema (arrowheads in **a**) consistent with metastatic disease to the brain. The patient underwent stereotactic radiosurgery Gamma Knife® (GK), and the MRI scan performed 1 month after treatment showed a significant decrease in the size of the nodule (arrows in **b** and **f**) and improvement of the surrounding vasogenic edema (arrowhead in **b**). Fifteen weeks after GK, the patient was started on immunotherapy (pembrolizumab), and 2 weeks after a new MRI scan was acquired. The third MRI scan showed a dramatic increase of the lesion size and enhancement (arrows in **c** and **g**), with central necrosis (*), and extensive vasogenic edema (arrowheads in **c** and **g**). Based upon the patient clinical picture and the imaging findings, treatment-related changes (radiation necrosis and pembrolizumab-induced pseudoprogression were the two main diagnostic considerations), and the patient was placed on steroids therapy. Follow-up MRI scan 2 weeks afterward demonstrated a progressive decrease in size, enhancement, and mass effect of the lesion (arrows in **d** and **h**), and gradual fading of the vasogenic edema (arrowheads in **d** and **h**)

progression. Rapid tumor cell proliferation increases the cell population density and semi-permeable cell membranes in a given voxel, resulting in a linear decrease of the water diffusivity and consequently a drop in the measured ADC values [63]. Necrosis, edema, and any pathological process break the semi-permeable membranes which decrease the cellular density and proportionally increase the ADC values [64–66]. Diffuse tensor imaging (DTI) is a variation of the DWI that captures additional information regarding the direction of water movement within voxels in the form of fractional anisotropy (FA) [64]. Necrosis causes loss of cellular structures and normal fibers, which in turn disrupt water diffusion, producing low-FA values. Interestingly, low-FA values are also expected in a growing tumor, owing to a disruption in surrounding parenchyma [67]. There is limited data regarding the utility of FA in differentiating cerebral radiation necrosis from tumor progression in primary and metastatic brain tumors.

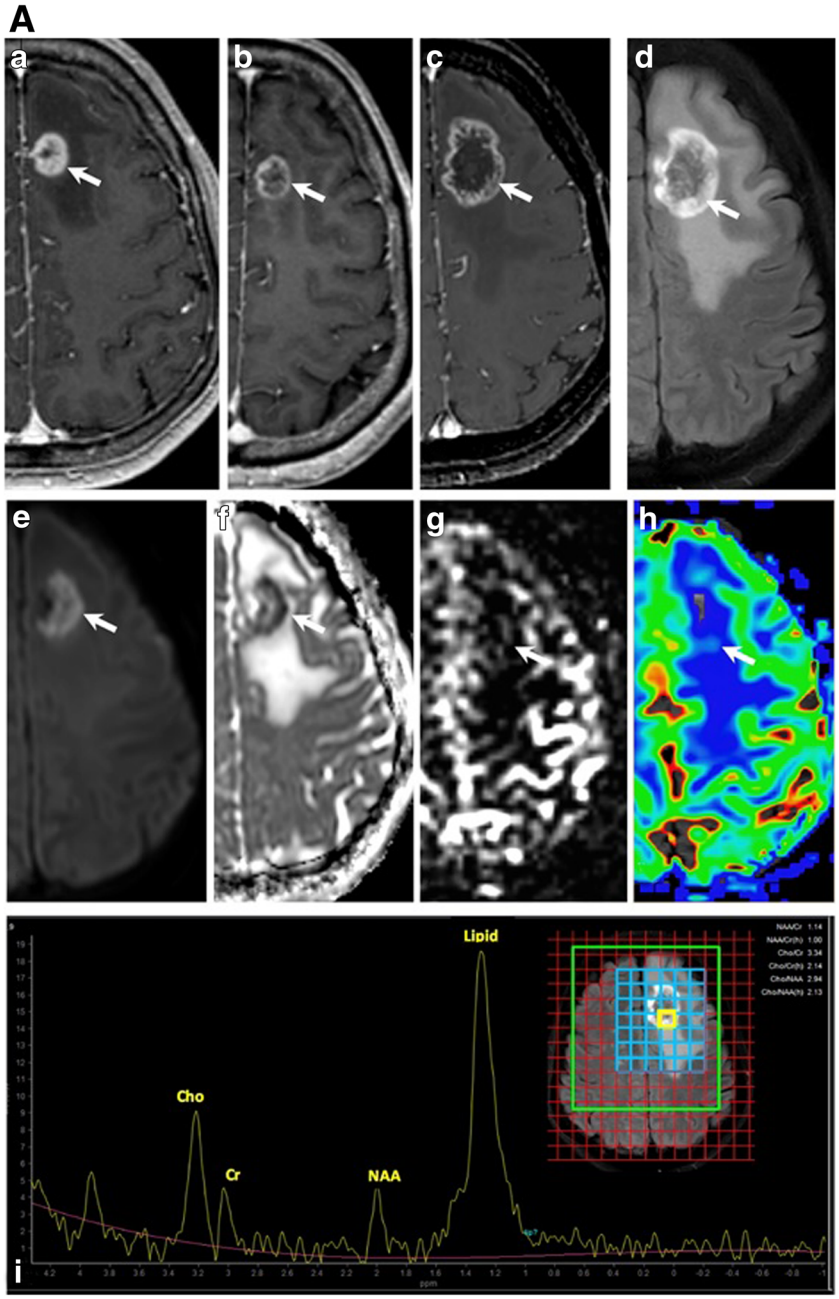
Perfusion-weighted imaging (PWI) consists of a group of MRI techniques that can quantitatively assess different brain hemodynamic variables such as relative cerebral blood volume (rCBV), cerebral blood flow (CBF), capillary permeability (Ktrans), mean transit time (MTT), and among others. rCBV is an imaging marker of neo-angiogenesis and is decreased in cerebral radiation necrosis (Fig. 4a). The ratio of the CBV values obtained from the target lesion and the contralateral normal tissue can be used to estimate tissue microvascular density and differentiate between cerebral radiation necrosis and tumor progression. Generally, recurrent tumors have been found to have an rCBV ratio of 2.5 and greater, whereas an rCBV ratio of < 0.6 has been associated with cerebral radiation necrosis [4]. An rCBV ratio of 2.1 has been found to be 90% sensitive and 80% specific, whereas a ratio of 3.69 is 100% sensitive and specific in differentiating tumor progression from cerebral radiation necrosis [68, 69]. There are at least three different MR perfusion techniques used in daily clinical

practice: dynamic susceptibility contrast (DSC), dynamic contrast enhancement (DCE), and arterial spin labeling (ASL), each one of them with its own strengths and weaknesses. DSC is acquired on T2-weighted images after rapid administration of intravenous contrast. DSC is widely available in clinical practice and provides excellent information about tumor hemodynamics validated in clinical research; however, this technique is particularly prone to susceptibility artifact from metal, blood, and air. DCE is a contrast-enhanced perfusion technique acquired on T1-weighted images which makes it less prone to susceptibility artifact; however, it requires advanced post-processing software and is not widely available. ASL is an MR perfusion technique that does not require intravenous administration of gadolinium, but its spatial resolution is low. DSC is the most commonly used PWI technique and it will be most appropriate in the vast majority of the cases.

MR spectroscopy is a non-anatomic imaging technique that determines the presence and concentration of various metabolites in a previously selected region of the brain. In the normal brain, metabolites such as N-acetyl aspartate (NAA; a marker of normal neuronal function) and choline (Cho; component of the cell membrane) are the dominant peaks in the spectroscopic graph (Fig. 4a and b). Thus, an alteration in the intracerebral metabolic composition (neuronal injury, neuronal plasticity etc.) would alter the relative concentration of those compounds [70, 71]. MRS can also detect lipids (Lip), which represent damage/necrosis. A ratio of MRS peaks can aide in accurate diagnosis and differentiation of cerebral radiation necrosis from tumor progression [4]. The NAA/creatinine (Cr; a marker of cellular energy reserves) ratio is higher with cerebral radiation necrosis compared to tumor progression, whereas Cho/NAA and Cho/Cr ratios are higher in recurrent tumors compared to necrotic lesions [72]. It is noteworthy that MRS requires long scan times since a large number of acquisitions are needed for accurate assessment and is a costly diagnostic modality. Novel MRS metabolite markers such as 2-hydroxyglutarate are under intense research; however, its clinical application is still limited [41].

Positron emission tomography (PET) is a nuclear imaging modality that involves intravenous administration of a radioactively labeled glucose (FDG). Tissues with high-glucose metabolic demand have higher FDG uptake and image conspicuity. Necrotic tissue has lower glucose metabolism, resulting in lower uptake of FDG. The caveat is that certain tumors such as low-grade gliomas also demonstrate low FDG uptake, overlapping with necrotic tissue [60]. This results in a high false-positive rate for cerebral radiation necrosis diagnosis, and a high false-negative rate in the setting of mixed lesions (cerebral radiation necrosis admixed with tumor progression). Multiple PET radiotracers besides FDG have been studied to address this issue (Supplementary Table). Of note, the minimum size of a target lesion for PET/CT is 1 cm^3, which is considered the threshold for an adequate diagnostic spatial resolution based on the distance that the positron travels before annihilation. Besides lesion size, other limitations of PET/CT include low-spatial resolution, false-positive increased tracer uptake due to an underlying inflammatory or infectious process, or location of the lesion close to inherent highly metabolic structures. Single-photon emission computed tomography (SPECT) provides three-dimensional information by imaging a target organ from multiple angles. Various radiotracers have been utilized in SPECT, the majority being technetium-based tracers which have high photon flux, providing better spatial resolution at lower radiation doses [60]. The drawbacks of SPECT include a relatively poor spatial resolution, preventing accurate localization of the radiotracer

Fig. 4 **A** RN. Sequential contrast-enhanced MRI scans of the brain from a patient in the sixth decade of life with history of lung adenocarcinoma. MRI of the brain with axial T1w images after intravenous contrast (a), (b), and (c), axial FLAIR (d), axial diffusion-weighted imaging (DWI) (e) with its corresponding ADC map (f), pseudo-continuous arterial spin labeling image (pCASL) (g), axial dynamic susceptibility contrast perfusion (DSC) (h), and Multivoxel MRI spectroscopy (i). The initial MRI scan shows a well-defined, centrally necrotic, heterogeneously enhancing nodule on the left superior frontal gyrus (arrow in a), associated with surrounding vasogenic edema, consistent with metastatic lung adenocarcinoma. The patient was treated with Gamma Knife. The lesion was stable in size on follow-up MRI examinations 10 months after treatment (arrow in b). However, 1 year after radiotherapy completion, the enhancing lesion started to grow (arrow in c and d), with interval increase of the mass effect and vasogenic edema. Advanced brain tumor imaging shows associated restricted diffusion (arrow in e and f) with quantitative ADC values non-suggestive of cellular proliferation. Perfusion imaging with pCASL and DSC does not demonstrate associated increase of the cerebral blood flow or cerebral blood volume respectively (arrow on g and h). The spectrum obtained by the MRI spectroscopy corresponds to the area highlighted by the yellow box on the blue grid on the localizer images (i). There is a decrease of choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) peaks in the suspicious area, associated with a high lipid peak (Lipi). The combination of findings on all advanced functional MRI techniques favored RN, which was further confirmed histopathological. **B** Tumor progression. MRI of the brain with contrast of a patient with diagnosis of glioblastoma IDH-wt. Follow-up MRI scan after completion of Stupp protocol with axial T1w image after intravenous contrast injection (a), and axial FLAIR (b) that show FLAIR hyperintensity surrounding the surgical bed (arrow in b) extending to the splenium of the corpus callosum (arrowhead in b). Three months after, there is a new focus of enhancement (compare the arrow in c with the arrow in a), associated with an increment of the FLAIR signal abnormality (compare d with b), concerning for tumor progression. Advanced MRI imaging shows restricted diffusion on diffusion-weighted imaging (arrows in e) suggestive of hypercellularity and focal increase in the cerebral blood flow values in the arterial spin labeling images (arrows in f). Multivoxel MR-spectroscopy shows an increase in the choline peak (Cho) and the decrease in the N-acetylaspartate (NAA) peak suggesting high cell membrane turnover and loss of neuronal integrity respectively. The above-described findings are consistent with tumor progression, which was confirmed histologically



uptake, as well as a low signal to noise ratio. Combining SPECT with CT had been thought to compensate for the shortcomings of SPECT. However, SPECT/CT did not attain popularity, owing to its high cost, ionizing radiation dose, and slow speed.

One Imaging Modality to Rule Them All?

Though the MRI characteristics of tumor progression and cerebral radiation necrosis are overlapping, differentiating features have been identified and are summarized above [73]. Qualitative assessment of the findings on conventional imaging carries the potential for interobserver variability [60]. Conversely, a quantitative approach could address the shortcomings of the current clinical practice but it is time and resource consuming and is not widely available [74]. The current literature supports that by combining structural and functional imaging modalities, the accuracy in discriminating between RN and tumor progression in lesions larger than 1 cm in the maximum diameter increases. A combination of MR perfusion imaging and MRS is potentially among the most appropriate combination imaging strategies in differentiating cerebral radiation necrosis from progression of primary and metastatic brain tumors [74].

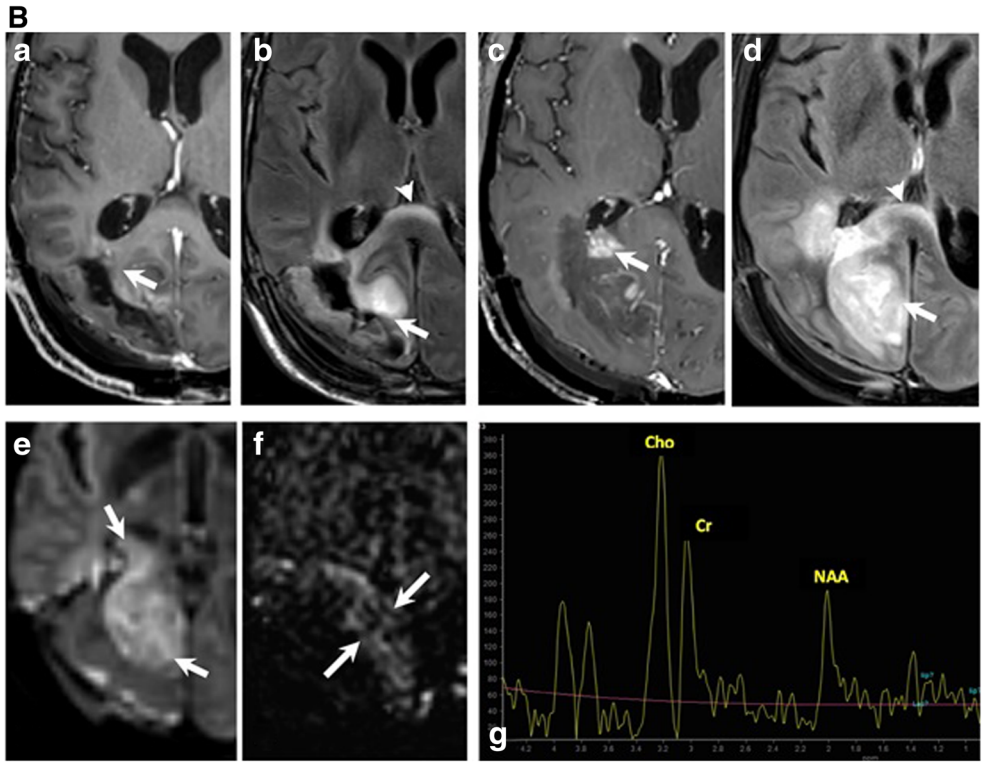


Fig. 4 (continued)

The Potential Role of Liquid Biopsy

Liquid biopsies may prove to be a safe and efficacious alternative to intracranial biopsies, which have a sampling error of up to 15% [75]. Koch et al. found that Annexin V-positive microvesicles (MV) that are shed into the bloodstream in GBM can be quantitatively assayed to differentiate between tumor progression and PsP [76•]. They found a lower MV count in blood samples of patients with PsP compared to the samples of patients with tumor progression. Another group of investigators studied the ratio of myeloid suppressor cell-derived biomarkers HLA-DR and vascular non-inflammatory molecule 2 (VNN2) expression on CD14+ monocytes, termed the DR-Vanin Index (DVI) [77]. They found that patients with cerebral radiation necrosis had a comparatively lower expression of HLA-DR and a high expression of VNN2, concluding that DVI was able to distinguish CRN from tumor progression with adequate certainty. These studies represent the preliminary evidence on the role of liquid biopsies in diagnosing radiation injury. Future studies could unravel the full potential of this emerging diagnostic modality. Studies have shown that it is possible to detect tumor-derived DNA and other biomarkers in the cerebrospinal fluid (CSF) of patients with brain tumors [78–80]. It is conceivable that the presence or absence of tumor DNA (or other biomarkers) in the CSF could be used in the future to help distinguish patients with cerebral radiation necrosis from patients with tumor progression [81].

Management of CRN

Patient symptomatology, performance and disease status, the frequency, dose, and duration of cancer therapy, as well as the time-dependent development of the suspected lesion(s) on diagnostic imaging, are important factors to consider when managing cerebral radiation necrosis. It is also paramount to involve patients and family members in the decision-making process, informing them of the natural course of cerebral radiation necrosis, the treatment modalities available, both established, and experimental and the possible outcomes [74].

Cerebral radiation necrosis may resolve spontaneously in some patients, though it can progress, evolving clinically or solely on diagnostic imaging, necessitating therapy [3]. For small and asymptomatic lesions, a watchful waiting strategy with serial clinical follow-up, supplemented with serial diagnostic imaging, can be employed. Close imaging follow-up is typically recommended at short intervals at first (every 6–8 weeks) until the lesion stabilizes or decreases in size. Follow-up may be increased or decreased, tailored on a case by case basis. The duration of follow-up should be governed by a multidisciplinary team consisting of the radiation oncologist, medical oncologist, neurologist, neurosurgeon, and the consulting radiologist. The probability of neuroradiological improvement ranges from 40% at 6 months to 76% at 18 months from the onset of radiological changes of cerebral

radiation necrosis [82]. Besides a watchful waiting strategy, treatment options range from supportive medical therapy to surgical excision of the necrotic lesion.

Medical Therapy

Corticosteroids are the first-line treatment for cerebral radiation necrosis. They inhibit the pro-inflammatory response that propagates cerebral radiation necrosis, including a reduction in the radiation-induced cytokine response, and improve BBB function, reducing the degree of edema. Dexamethasone is commonly prescribed owing to its immunomodulatory effect and the lack of salt retention seen with the use of hydrocortisone [83, 84]. Pulsed corticosteroid administration is effective in curtailing the symptoms of cerebral radiation necrosis in the short term [85]. However, the value of corticosteroids is transient and supportive rather than curative. An additional caveat is the array of adverse events associated with long-term steroid therapy, as well as the risk of steroid dependency. We typically use doses of dexamethasone ranging from 4 to 16 mg/day divided into once or twice daily dosing for 4–6 weeks with a gradual taper. It is crucial to recognize steroid refractory cerebral radiation necrosis in a timely manner, and consideration should be given to additional or alternative therapies as early as possible, in order to prevent side effects from prolonged steroids use such as myopathy, gastrointestinal bleeding, infections (oral thrush and pneumocystis pneumonia), steroid-induced psychosis, and adrenal insufficiency. Patients who do receive corticosteroid therapy should be prescribed daily proton pump inhibitors for prophylaxis against GI bleeding and trimethoprim/sulfamethoxazole (TMP-SMX) for prophylaxis against PCP when ≥ 4 weeks of high-dose corticosteroid therapy (≥ 30 mg/day of prednisone or equivalent of other formulations) is planned.

A variety of drugs have shown efficacy in the treatment of cerebral radiation necrosis, ranging from vitamin E supplementation to targeted antiangiogenic agents (Table 1). Bevacizumab, an anti-VEGF antibody, is the only therapy proven to be effective for cerebral radiation necrosis in a RCT [93]. Bevacizumab counters the effects of VEGF on the propagation of cerebral radiation necrosis, is associated with a decrease in the enhancement of necrotic lesions on imaging, has a favorable adverse effect profile, and enables reduction of steroid use [94]. Preliminary data has emerged on the utility of intra-arterial administration of bevacizumab, successfully treating cerebral radiation necrosis with sustained response 8.5 months post-administration. An RCT is underway to validate this route of administration for treatment of cerebral radiation necrosis [95]. Re-challenging patients with bevacizumab has been shown to be effective in treating cerebral radiation necrosis among patients previously treated with bevacizumab. However, the only published RCT on the utility of bevacizumab in managing cerebral radiation necrosis had merely enrolled 11 patients in the bevacizumab arm, 6 of whom developed an adverse event, including one case of pulmonary embolism, and one superior sagittal sinus thrombosis. Hence, the safety of bevacizumab warrants further validation with large-scale RCTs.

The use of anticoagulants to treat cerebral radiation necrosis is reported in the literature, though the body of evidence is very limited [86]. Hence, the efficacy and safety of using heparin or warfarin in the setting of cerebral radiation necrosis is questionable. Pentoxifylline, a methylxanthine derivative which modifies blood viscosity, has been shown to minimize diffusion capacity of the lungs for carbon monoxide in lung cancer and breast cancer patients treated with RT [96]. In patients with head and neck squamous cell carcinoma, pentoxifylline has been shown to reduce skin changes, fibrosis, and soft tissue necrosis caused by post-operative RT [97]. The use of pentoxifylline for cerebral radiation necrosis has shown a variable effect on mitigation of radiation injury [87]. A clinical trial assessing the prophylactic administration of pentoxifylline and vitamin E for prevention of cerebral radiation necrosis is expected to report findings in the near future [98].

A recent phase II study aimed to outline the utility of nerve growth factor (NGF) for the treatment of cerebral radiation necrosis [85]. NGF was able to curtail the symptoms of cerebral radiation necrosis for a longer duration compared to corticosteroids. Though promising, NGF is currently not the standard of care and further investigation to validate its safety and efficacy is warranted.

Hyperbaric Oxygen Therapy

The rationale for using HBOT to treat cerebral radiation necrosis is that increasing the oxygen concentration would stimulate angiogenesis, restoring the blood supply of the necrotic lesion, thereby promoting healing. Patients receive HBOT in a chamber with 100% oxygen at 2.5 times atmospheric pressure, up to 5 times a week. This cycle can be repeated for up to 40 sessions. HBOT has shown to reduce cerebral radiation necrosis from 20 to 11% when administered prophylactically, 1 week after SRS for 20 sessions [99]. However, the evidence is limited to case reports, with no RCTs published and one RCT underway [100, 101].

Surgical Resection

Cerebral radiation necrosis refractory to medical therapy may require surgical intervention to relieve mass effect (Fig. 5). Despite surgical resection, edema beyond the necrotic lesion

Table 1 Treatment modalities for the management of radiation necrosis

Management modality	Rationale	Advantages	Pitfalls	Clinical trials done
Steroids	Minimizing cerebral edema	Cheap and widely available	Steroid dependency and adverse events*	No
Anticoagulants [86]	Mitigate radiation-induced vascular stenosis Inhibit platelet aggregation Inhibit neutrophil chemotaxis and release of cytokines	Cheap Concurrent DVT prophylaxis	Risk of hemorrhage Limited body of evidence	No
Pentoxifylline [87]	Decreases the levels of TNF-α and interleukin-1β following brain irradiation; inhibits upregulation of VEGF	NA	May enhance antiplatelet/anticoagulant effect of drugs	No
Vitamin E [87]	Scavenges reactive oxygen species Protects cell membranes against lipid peroxidation Promotes connective tissue repair	NA	Potential for vitamin E toxicity	No
Bevacizumab [92]	Mitigates VEGF-mediated progression of RN	Only medical treatment with level l evidence	Hypertension Risk of renal dysfunction Risk of thrombotic/ischemic events	Yes
Hyperbaric oxygen therapy [89]	Stimulating angiogenesis within RN lesions by increasing oxygen concentration	Decreased duration of steroid therapy Reduction in cerebral edema	Barotrauma Increased risk of seizures	No
Surgery [90]	Relieves intracranial pressure Allows or resection of lesion	Immediate symptomatic relief and cure	Surgical morbidity/mortality Limited by lesion location ➔ deep-seated lesions cannot be surgically resected	No
Laser interstitial thermal ablation [91, 92]	Laser-induced vascular sclerosis mitigates progression of RN	Can treat deep-seated lesions	Limited data	No

*Notable side effects include steroid dependency, steroid-induced myopathy, gastrointestinal bleeding, and infections including oral thrush and pneumocystis pneumonia, steroid-induced psychosis, and steroid-induced adrenal insufficiency with chronic use

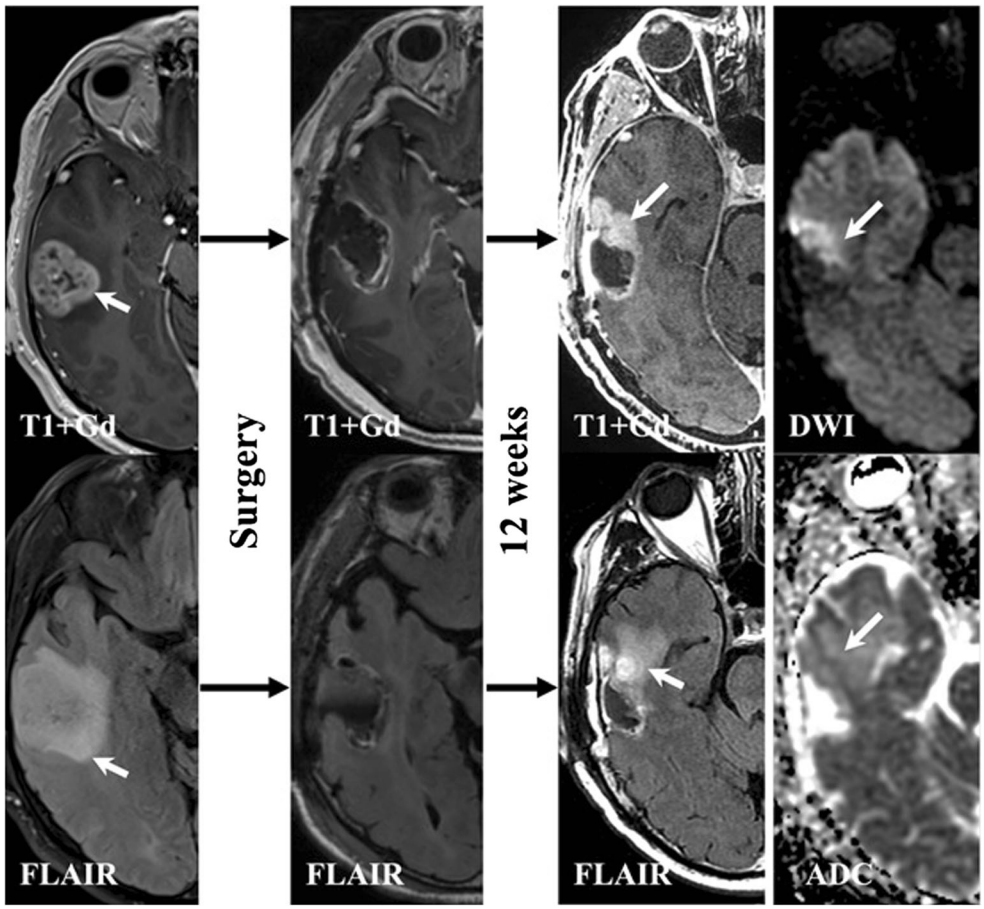


Fig. 5 Pseudo-progression. Serial images from a patient with diagnosis of glioblastoma IDH-wt of the right temporal lobe. On the left column, the baseline MRI scan shows a heterogeneously enhancing, ill-defined, centrally necrotic mass, centered in the right temporal lobe, with surrounding FLAIR hyperintensity corresponding to glioblastoma. The second column corresponds to the immediate postoperative scan that shows complete macroscopic resection of the enhancing and non-enhancing portions of the tumor. The third column corresponds to a follow-up MRI scan 12 weeks after completion of the standard-of-care treatment showing a concerning new area of enhancement and FLAIR hyperintensity along with the anterior border of the surgical bed (arrows). There is no associated restricted diffusion on the DWI and ADC images. Pathological examination proved that the new area of enhancement corresponded to treatment changes (pseudo-progression)

may take a few weeks to resolve and should be monitored closely. [102]. Additionally, surgery can provide tissue diagnosis and the ability to study samples to rule out tumor progression which may be missed on biopsy. It is important to choose surgical candidates wisely, since patients often have been pretreated heavily, have multiple comorbidities, and may have an unfavorable performance status, which puts them at a high risk for surgical morbidity, particularly wound-related complications and potential mortality. The ideal surgical candidate should have a favorable performance status, accessible location of the necrotic mass, minimal or no comorbidities, and one who has failed medical therapy.

Laser Interstitial Thermal Ablation

Laser interstitial thermal ablation (LITT) relies on the delivery of laser electromagnetic radiation to targeted tissue, which absorbs photons, leading to a release in thermal energy. This heat is then redistributed through convection and conduction, leading to coagulative necrosis of the lesion. Currently, there are two commercially available LITT systems [90, 102]. The NeuroBlate System (Monteris Medical Inc., Winnipeg, Canada), which consists of pulsed diode laser (12 W) that can integrate with intraoperative MRI suites as well as conventional MRI machines. Visualase (Medtronic Inc., Minnesota, MN) is another LITT system which is also MRI-integrated and is fitted with a diode laser which has an output of 15 W.

LITT can be a promising treatment modality in lesions that are difficult to access surgically. The utility of LITT in the setting of cerebral radiation necrosis is currently limited, but has shown significant improvement of symptoms as well as resolution of the necrotic focus in cases that have been reported [91]. No RCTs studying LITT as a treatment for cerebral radiation necrosis have been published to date.

Conclusion

The risk of cerebral radiation necrosis varies with the RT modality, dose, dose fractionation, the tumor histology, the genetic make-up of the tumor, and individuals' genetic susceptibility to radiation injury. It is crucial to standardize structural and functional imaging strategies used to diagnose, grade, and monitor the disease course. Novel diagnostic modalities such as liquid biopsies can potentially increase the diagnostic accuracy for cerebral radiation necrosis, though further research is needed before clinical implementation is possible. Therapeutic options for the treatment of cerebral radiation necrosis are increasing, particularly, bevacizumab and laser interstitial thermal therapy, which highlights the need for active research in this field including the development of accurate and cost-effective diagnostic and treatment algorithms. With the advent of novel cancer therapies (targeted therapy, immunotherapy, viral therapies), the survival of patients with advanced malignancies is expected to improve along with an increased prevalence of cerebral radiation necrosis. Hence, attention should be given to treatment-associated adverse events, their timely diagnosis, treatment, and impact on the patients' quality of life.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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