Cerebral radiation necrosis: diagnostic challenge and clinical management

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Summary. Cerebral radiation is an indispensable cornerstone in the treatment of many primary and metastatic brain tumors. However, besides its desired therapeutic effect on tumor cells, a significant proportion of patients will experience neurotoxic side effects as the consequence of radiotherapy. Radiation necrosis can result in progressive neurological symptoms and radiographic changes. To differentiate radiation necrosis from progressive tumor based on imaging can pose a diagnostic challenge because the MRI characteristics may be similar in both situations. Therefore, surgical biopsy and pathological confirmation is sometimes necessary to guide further management. Effective treatment options for cerebral radiation necrosis exist and should be offered to symptomatic patients. A better understanding of the cellular and molecular processes underlying the development of radiation necrosis is necessary to prevent and minimize radiation-associated morbidity and to improve treatment strategies.

Key words. Bevacizumab. Complications. Glioma. Management. Radiation necrosis. Review. Steroids.

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Introduction

Radiation therapy is an indispensable component of the treatment of primary and metastatic brain tumors [1,2]. Different treatment modalities such as involved field radiotherapy (IFRT), whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) have been developed and optimized with regards to treatment dose, fraction size and fractionation schedule in order to maximize the therapeutic effect on the tumor while at the same time minimizing the side effects on normal brain tissue. Despite these efforts, a significant proportion of patients will experience treatment related neurotoxicity, such as cerebral vasculopathy and radiation necrosis.

While the exact pattern and risk factors of radiation induced tissue necrosis remain poorly understood, associated neurological signs and symptoms can be severe and progressive and may contribute to significant treatment related morbidity and even mortality. In addition, the clinical and radiographic presentation of cerebral radiation necrosis is often indistinguishable from progressive tumor, and therefore represents a major diagnostic challenge in patient management.

Generally, radiation related neurotoxicity may occur in form of acute, early-delayed and late-delayed side effects based on the time of onset and clinical presentation [3,4]. However, these categories are defined somehow arbitrarily and in clinical practice may have significant overlap. Acute effects usually occur during or within a few weeks after the start of radiation and are characterized by signs of increased intracranial pressure (ICP), such as headaches, nausea and emesis. Early-delayed side effects typically occur within the first 3-6 months of radiation and present with somnolence and fatigue. Late-delayed radiation-induced side effects occur months to years after radiation and can present as diffuse leukoencephalopathy, cerebral radiation necrosis or vascular abnormalities. While acute and early-delayed effects of radiation toxicity are typically reversible, chronic side effects may lead to persistent and progressive symptoms and typically require therapeutic interventions [5,6].

A unique form of 'treatment-related effects' of combined chemotherapy and radiation, typically seen in patients with malignant gliomas, has been termed 'pseudo-progression' and usually occurs within 1-6 months after the start of therapy [5,7]. Pseudo-progression is defined as an increase in the amount of nodular enhancement usually seen within the main radiation field, and which can be associated with significant mass effects and clinical neurologic symptoms. The pathophysiology of pseudo-progression is not well understood but likely different from the classical form of late-delayed radiation induced tissue necrosis [3,4]. In this present review, we will focus on the clinical picture and challenges of late-delayed radiation necrosis.

Delayed radiation necrosis

Cerebral radiation necrosis frequently occurs within 12 months after treatment, though there is a significant range in its onset, and radiation necrosis even more than 10 years after completion of radiation has been described [4,8]. The exact incidence and prevalence of radiation necrosis is not well characterized. One of the reasons for the limited understanding of radiation necrosis has at least in part to do with the significant challenge in establishing a correct diagnosis based on imaging criteria. In addition, there is an ongoing debate about the risk factors that are associated with developing radiation necrosis. Ruben et al found the overall incidence of radiation necrosis to be 4.9% in patients with high-grade gliomas treated with radiation either alone or in combination with chemotherapy. One report suggests that approximately 6.5% of patients receiving a total radiation dose of 60 Gy in 30 fractions will develop radiation necrosis [9]. Stereotactic radiosurgery, which has been commonly used in the treatment of arteriovenous malformations and brain metastases, carries a higher risk of radiation necrosis with reported incidences in the range of 14 to 24% [10,11]. However, there is significant variability in the incidence of radiation necrosis based on radiation parameters [11]. With the limited data that is available, it appears that the majority of patients are asymptomatic, though neurological symptoms occur in at least 14-20% of patients [10]. Notably, temporal lobe necrosis is a well-described late radiation-related complication in up to 37% of patients receiving radiotherapy for nasopharyngeal cancers [12,13]. The current body of literature suggests that the most important risk factors to develop radiation induced tissue necrosis include radiation modality, radiation dose, treatment volume and fraction size [9-12,14, 15]. In addition, concurrent or adjuvant chemotherapy further increases the risk of cerebral radiation necrosis [9,16-18].

Pathophysiology

The cellular and molecular pathophysiology of radiation associated tissue necrosis is complex and only incompletely understood. A combination of vascular and glial cell injury and a reinforcing inflammatory component have been suggested as key mechanisms [6]. Radiation-induced endothelial cell injury leads to breakdown of the blood brain barrier (BBB) and results in vasogenic edema and hypoxia [19]. Hypoxia in turn leads to upregulation of various cytokines, such as hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor (VEGF) [20,21]. HIF-1α and VEGF, presumed to be secreted by reactive astrocytes in the necrotic core and the peri-necrotic tissue of the lesion, further increase the vascular permeability and lead to subsequent ischemia and formation of fibrinoid tissue necrosis. VEGF production in the peri-necrotic lesion seems to play a crucial role, as the degree of VEGF production correlates with the degree of necrosis [22]. In addition to the direct endothelial cell damage, radiation induces ceramide-mediated apoptotic pathways within endothelial cells, thereby further aggravating vascular injury and vasogenic edema [23]. Astrocytes, oligodendrocytes and oligodendrocyte precursor cells are damaged either directly by radiation, or indirectly by ischemia and the associated inflammatory response in the surrounding tissue [24]. A major component of the inflammatory response is the release of TNF-α and of other pro-inflammatory cytokines that attract lymphocytes, granulocytes and fibroblasts to further upregulate VEGF production [21,25,26].

Clinical presentation and diagnostic challenge

The clinical signs and symptoms associated with cerebral radiation necrosis are variable based on location and degree of tissue injury and the amount of associated peri-lesional edema. Patients therefore can present with progressive focal neurological deficits and seizures, or can be asymptomatic and present with radiographic changes only. Similar to the imaging appearance associated with tumor progression, magnetic resonance imaging (MRI) typically reveals focal areas of contrast-enhancement on T_1-weighted images and T_2/FLAIR hyperintensities reflecting peri-lesional edema (Figs. 1 and 2). A reliable distinction between radiation necrosis and tumor is therefore usually not possible despite significant efforts to identify MRI characteristics attributable to the one or the other entity [27-29].

Because of its importance for patient management, the use of various advanced imaging modalities is currently being investigated [30].

MR perfusion studies, using dynamic susceptibility contrast enhanced perfusion MRI (DSC-MRI), might be able to distinguish true tumor progression from tissue necrosis based on the higher relative cerebral blood volume (rCBV) seen in solid tumor tissue as compared to normal brain. In contrast, areas of tissue necrosis usually have lower rCBV levels

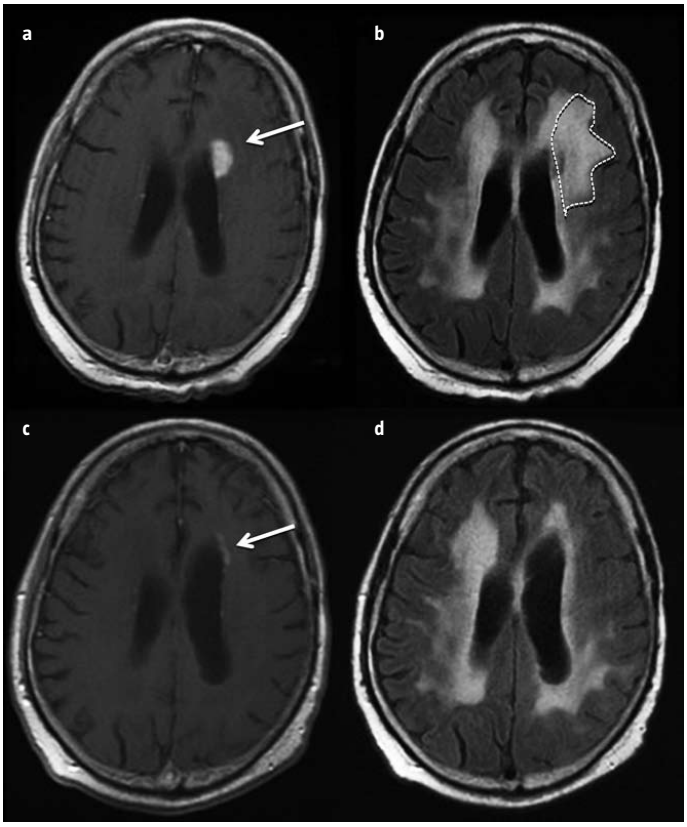
when compared to normal brain [31-33]. In addition to rCBV, other hemodynamic parameters such as relative peak height (rPH) and percentage of signal-intensity recovery (PSR) have been evaluated in clinical and experimental studies [32,34]. Despite the promising results from several studies, the use of DSC-MRI is hampered by the current lack of standardization of data acquisition and processing and its sensitivity to susceptibility artifacts caused by hemorrhage and surgical hardware [35].

MR spectroscopy (MRS) is another imaging technique that has been proposed to be helpful in distinguishing tumor from necrosis by analyzing the relative composition of various metabolites, such as N-acetyl aspartate (NAA), choline (Cho), Creatine (Cr), and lactate (Lact). Tumors were shown to correlate with higher Cho/Cr and Cho/NAA ratios, whereas radiation necrosis has been associated with higher Lact/Cr and lower Cho/Cr ratios [36-38] The use of MRS is limited by its low spatial resolution and its inability to accurately classify lesions characterized by mixed tumor and necrosis [39].

Positron emission tomography (PET) uses the uptake of radioactive labeled metabolites such as ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) to differentiate between metabolically active tumors and metabolically less active areas of necrosis [40]. However, it can be difficult to differentiate small areas of metabolically active tumors from the background of already highly metabolically active brain [30]. Therefore, amino-acid analogs such as ^{18}F-DOPA and ^{11}C-MET may represent more reliable metabolites with less metabolic activity in the normal brain [41-44].

Collectively, there is currently no established imaging modality available that has proven to be sufficiently sensitive and specific in order to reliably differentiate between progressive tumor and treatment-related changes. Therefore, surgical tissue resection and histopathological evaluation often remains necessary to establish a correct diagnosis and guide patient management.

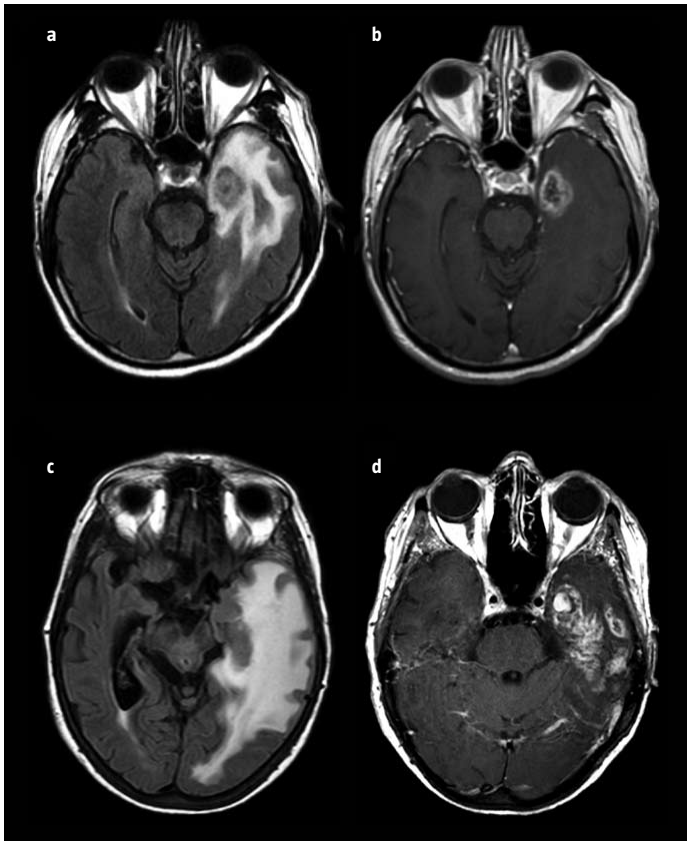
Figure 1. Delayed radiation necrosis in a patient with malignant glioma. Axial magnetic resonance imaging (MRI) from a 67-year-old patient with diffuse infiltrating glioma (WHO grade III) involving the left fronto-temporo-parietal region. Three years after conventional photon radiation therapy, the patient developed a new, left-periventricular enhancing lesion on T_1-post gadolinium images (a, arrow) along with new abnormal T_2/FLAIR signal hyperintensity (b, dotted line), suggestive of cerebral edema. Over the course of 12 months and without additional therapy, the area of abnormal enhancement fades (c, arrow), along with a decrease in T_2/FLAIR hyperintensity surrounding this lesion (d), consistent with resolving radiation associated tissue injury. Note, that the MRI also demonstrates subcortical leukoencephalopathy secondary to prior radiation, which remains stable over the course of 12 months (b and d).



Pseudo-progression

Pseudo-progression characterizes a well-described phenomenon in patients with high-grade glioma treated with radiation and chemotherapy, in which radiographic changes such as new areas of contrast enhancement and edema occur early (usually within 3 months) after treatment [5,45,46]. These radiographic changes can be accompanied by clinical deterioration but often remain asymptomatic and stabilize and resolve spontaneously (Fig. 3). Based on studies with pathological confirmation, it is estimated that pseudo-progression occurs in 21-31% of patients with high-grade glioma treated with radiation and concomitant and adjuvant temozolomide [7,46]. Brandes et al found a correlation between pseudo-progression and the MGMT methylation status of the tumor. In this study, up to 91% of high-grade glioma patients that developed pseudo-progression had tumors with methylated MGMT promotor status. Both, methylated MGMT promotor status and development of pseudo-progression were associated with longer progression free and overall survival

Figure 2. Delayed radiation necrosis in patients with head and neck cancer. (a, b): 58-year-old patient with nasopharyngeal carcinoma treated with radiation therapy. Axial magnetic resonance images (MRI) demonstrate abnormal T_2/FLAIR hyperintensities in the left temporal lobe (a) four years after radiation therapy, along with a focus of abnormal enhancement (b), consistent with delayed radiation necrosis. (c, d): 65-year-old patient with adenocarcinoma of the left auditory canal treated with adjuvant proton radiation. Five years later, axial MRI reveals an extensive area of abnormal T_2/FLAIR hyperintensity in the left temporal lobe (c), along with irregular-nodular enhancement (d). Findings were consistent with tissue necrosis and leukoencephalopathy as delayed effects from prior radiation therapy.



rates [7]. Despite the correlation of MGMT methylation status and the incidence of pseudo-progression, subsequent studies could not confirm the effect on progression-free and overall survival rates [46,47]. Based on these results, it is current clinical practice to continue treatment with temozolomide in cases of radiographic changes within the first 3 months of therapy [5]. It has been hypothesized that pseudo-progression represents a form of radiation induced tissue injury which can be potentiated by the synergistic use of chemotherapy and defective DNA repair mechanisms such as the methylated MGMT promotor status [5,7]. However, it needs to be emphasized that pseudo-progession likely represents a unique scenario encountered in patients with high-grade glioma treated with radiation and chemotherapy. The pathophysiology of pseudo-progression is not well understood and the clinical and radiographic course may be different from what is described for delayed onset of cerebral radiation necrosis.

Clinical management

Only few treatment options for patients with focal cerebral radiation necrosis exist and their use can be tailored depending on the clinical presentation and the degree of tissue injury. For clinically asymptomatic patients, close clinical and radiographic monitoring may be sufficient as focal lesions may stabilize and spontaneously resolve over time without medical or surgical intervention [6,10].

Corticosteroids

For patients with progressive neurological symptoms, or in case subsequent imaging reveals worsening edema and mass effect, treatment with corticosteroids is often effective [48,49]. Corticosteroids reduce the production of pro-inflammatory cytokines and help to normalize BBB function with a consequence of reducing vasogenic edema and improvement in clinical symptoms [49,50]. However, corticosteroids are associated with numerous and well known neurological and medical side effects, such as immunosuppression, mood alterations, cognitive impairment, myopathy, obesity, osteopenia and hyperglycemia, which are limiting the long-term use [51].

VEGF targeted agents

Given the crucial role of VEGF in the pathophysiology of radiation necrosis, targeting VEGF has been proposed as a powerful treatment strategy because of its potential to restore the integrity of the blood brain barrier and subsequent reduction of cerebral edema [52]. In a small double-blind randomized placebo-controlled clinical trial, treatment with the VEGF-targeting antibody bevacizumab resulted in clinical and radiographic improvement in patients with biopsy-proven radiation necrosis refractory to corticosteroids [53]. Other groups have confirmed the successful use of bevacizumab for cerebral radiation necrosis at doses of 5-10 mg/kg every 2-3 weeks [54-57]. However, the significant costs of VEGF tar-

geting agents and the associated clinical risks such as deep venous thrombosis, pulmonary embolism and bleeding need to be carefully weighed against the possible benefits. One case report described worsening of neurological function after the use of bevacizumab. The authors hypothesized that VEGF-targeted therapy may lead to 'overpruning' of at-risk vasculature within the radiation field and therefore may cause subsequent hypoxia and necrosis [58].

Antiplatelet therapy, anticoagulation and hyperbaric oxygen

The use of the antiplatelet agent pentoxifylline in combination with Vitamin E as treatment for cerebral radiation necrosis following SRS was evaluated in a small pilot study. Williamson et al reported reduction in peri-lesional edema secondary to pentoxifylline [59]. Based on these results and the benefit in preventing radiation-related tissue damage in other organs [60], the prophylactic use of pentoxifylline and vitamin E in patients undergoing stereotactic radiosurgery for metastatic brain tumors is currently investigated in a phase II clinical trial (NCT01508221).

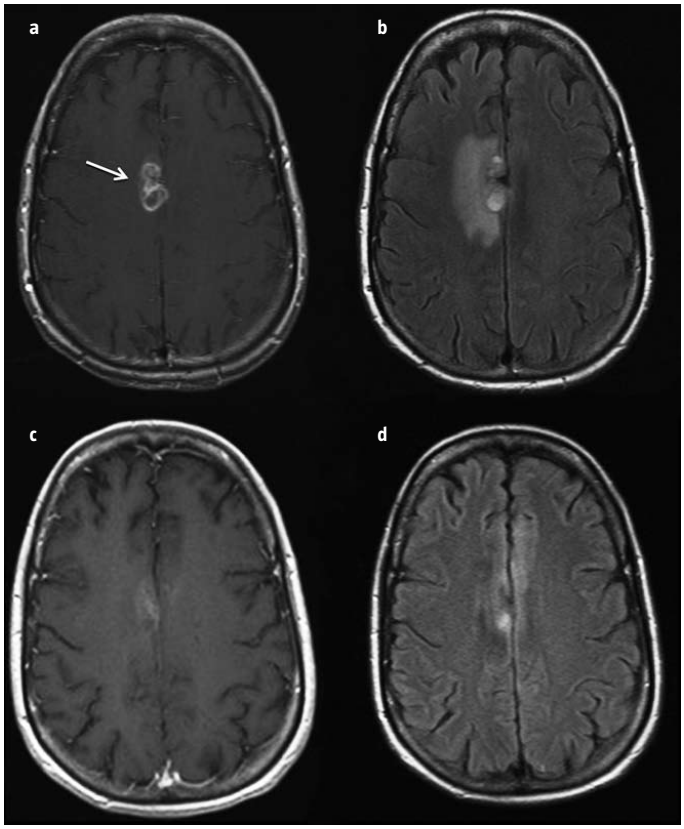
In addition, few case reports have postulated the successful use of anticoagulation [61] and hyperbaric oxygen [62] for treatment of cerebral radiation necrosis. However, the efficacy of these treatment modalities remains unclear and has not been validated in subsequent studies.

Minimally invasive and surgical treatment options

Recent reports suggest a potential role for laser interstitial thermal therapy (LITT) in the treatment of focal cerebral radiation necrosis. Initial studies have demonstrated successful use of LITT in patients refractory to steroids, in necrotic lesions not considered accessible for surgical resection based on their location and in patients with contraindications for using bevacizumab [63,64]. Under real-time MRI guidance, thermal energy is delivered to the lesion site via a laser probe. Focal heat administration results in effective tissue ablation of the necrotic core and the VEGF-rich peri-necrotic zone of the lesion, thereby successfully blocking the pathophysiological cascade of radiation-induced tissue necrosis [65]. The current literature suggests that LITT is a promising technology for this indication and is considered overall safe and effective [63-65]. LITT is currently under investigation in several clinical trials, such as in a phase II clinical trial in patients with cerebral radiation necrosis after stereotactic radiosurgery (NCT01651078).

Lastly, in patients with progressive neurological decline due to significant mass effect and impending herniation, conventional surgical resection of the necrotic mass may be beneficial. Surgical resection also can be a very reasonable diagnostic and therapeutic strategy in order to optimize and guide treatment [66].

Figure 3. Pseudo-progression in a patient with malignant glioma. Axial magnetic resonance imaging (MRI) from a 61-year-old patient with anaplastic astrocytoma WHO grade III, centered in the right cingulate gyrus and treated with gross total resection and adjuvant chemotherapy and radiation. 3-4 months after completion of chemoradiation, the patient develops a new, heterogeneously enhancing lesion on T_1-post gadolinium images in the location of the prior resection cavity (a, arrow) with associated increase in surrounding T_2/FLAIR signal hyperintensity (b), suggestive of cerebral edema. Both the abnormal enhancement (c) and the associated cerebral edema (d) spontaneously resolve over the course of 2-3 months without adjuvant therapy, consistent with resolving pseudo-progression.



Summary and conclusion

Cerebral radiation is an indispensable cornerstone

in the treatment of many primary and metastatic brain tumors. However, besides its desired therapeutic effect on tumor cells, cerebral radiation can lead to damage of normal brain, which can result in progressive neurological symptoms and radiographic changes. A detailed understanding of the underlying cellular and molecular processes as well as the available treatment modalities is therefore necessary to prevent and minimize radiation-associated morbidity and mortality. Further research is necessary to develop reliable imaging strategies, which are capable of distinguishing progressive tumor from treatment related changes. To overcome this diagnostic challenge will be an important step in guiding and improving the medical care for these patients.

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Necrosis cerebral por radiación: desafío diagnóstico y tratamiento clínico

Resumen. La radioterapia cerebral es una de las piedras angulares del tratamiento de numerosos tumores cerebrales primarios y metastásicos. Pese a ello, aparte de su efecto terapéutico deseado sobre las células tumorales, una parte sustancial de los pacientes sufre efectos secundarios de carácter neurotóxico a consecuencia de su aplicación. La necrosis por radiación puede provocar síntomas neurológicos y cambios radiográficos progresivos. Diferenciarla de la progresión tumoral en las imágenes puede llegar a ser un verdadero reto, dada la similitud que en ocasiones presentan las características de la resonancia magnética en ambas situaciones. Por esa razón, a veces es necesario recurrir a la biopsia quirúrgica y la confirmación histopatológica para confirmar el diagnóstico y orientar el tratamiento. Existen opciones eficaces de tratamiento para la necrosis cerebral por radiación y los pacientes con síntomas deben recibirlas. Es preciso ampliar el conocimiento sobre los procesos celulares y moleculares que se esconden detrás del desarrollo de la necrosis por radiación si se quiere prevenir y minimizar la morbilidad asociada a ella y mejorar las estrategias terapéuticas disponibles.

Palabras clave. Bevacizumab. Complicaciones. Corticoesteroides. Glioma. Necrosis por radiación. Revisión. Tratamiento.