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Diagnosis and Management of Radiation Necrosis in Patients with Brain Metastases and Primary Tumors

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Abstract

The incidence of radiation necrosis has increased secondary to combined modality therapy for brain tumors and stereotactic radiosurgery. The pathology of progressive brain radiation necrosis (RN) primarily includes inflammation and angiogenesis in which cytokines, chemokines, and vascular endothelial growth factors are upregulated. Combined multiparametric imaging, including lesional metabolism, spectroscopy, and blood flow, could enhance diagnostic accuracy compared with a single imaging study. Nevertheless, a substantial risk of bias restricts firm conclusions about the best imaging technique for diagnosing brain RN. Bevacizumab shows promising results of improving radiographic edema and post-gadolinium enhancement with associated symptomatic improvement. However, this was based on small double-blinded randomized controlled trials, which introduces a high risk of bias due to the small sample size despite the high-quality trial design. Etoricoxib combined with corticosteroids also resulted in a more significant reduction in radiographic edema than corticosteroids alone but had no impact on reducing the enhancing lesion. There is a great need for further prospective randomized controlled trials (RCTs) to treat brain RN.

Keywords: radiation necrosis, brain metastases, brain tumors, gliomas, brain injury

1. Introduction

For years, radiation therapy (RT) has played a critical role in the treatment of primary brain tumors (PBT) and brain metastases (BM). Different techniques can be used depending on the clinical setting, including brachytherapy, fractionated stereotactic radiotherapy, and stereotactic radiosurgery. The use of RT in brain tumors has been related to improved progression-free survival as well as overall survival, especially in patients with high-risk low-grade gliomas [1]. As with different cytotoxic treatment approaches, the use of cranial irradiation comes with

the possibility of specific side effects known as radiation toxicity that can be acute (early toxicity) or late. Usually, early toxicity symptoms are reversible and treatable with proper supportive care; these symptoms include fatigue, headache, alopecia, dermatitis, nausea, and vomiting. Radiation necrosis (RN) is one of the leading late toxicity clinical manifestations. It usually occurs between 1–3 years after RT in the location that received the most radiation (tumor location) or a nearby area.

Clinical manifestations of RN will depend on the location of its development [2]. Signs and symptoms of focal neurologic deficits might occur, seizures are also present in approximately 20% of patients [3]. Depending on the region of the brain that is affected, different sets of symptoms might be present, including but not limited to motor deficits (2.9%), sensory deficits (1.3%), cognitive deficits (1%), speech deficits (1.3%), visual disturbances (0.6%), ataxia (1.6%) and general symptoms like headache (5%), nausea (1%) and hemorrhage (5%) [4]. This chapter will discuss the epidemiological features of RN, its risk factors, its pathophysiology, its diagnosis, and treatment.

2. Incidence of radiation necrosis

The current true incidence of RN is hard to estimate. According to Vellayappan *et al.*, the incidence of this kind of toxicity might vary between 5–25% [5]. This broad range is mainly explained, but the different methodologies used in epidemiological studies of RN in which its definition is not homogenous and only some studies have required histological confirmation, the studies' follow-up can also provide different results. The kind of RT provided, the dosing, and the fractionation of radiation might also impact the incidence of RN [6].

In a study made by Kohutek *et al.*, the evidence of RN (including asymptomatic cases) was 25.8%, with a progressive increase in actuarial incidence regarding the time of evaluation as follows: 5.2% at six months after RT, 17.2% at 12 months, 23% at 18 months and 34% at 24 months. The median time to the first diagnosis of RN was 10.7 months. In this study, the incidence of symptomatic RN was 11.8% at 12 months. Significant variability in diagnostic methods used in this study was seen, with some patients being diagnosed histologically, some via FDG-PET and others by MRI alone [7]. Another study conducted by Blonigen *et al.* analyzed RN in metastatic lesions after stereotactic surgery; a total of 63 patients with 173 lesions were studied. 14% of the lesions presented with RN, 10% were symptomatic. The individual factor related to a higher risk for RN, whether symptomatic or asymptomatic, was an increased dose of radiation. The location of the lesion was not related to the development of RN of any kind [8].

Studies where pathological confirmation of RN was done reported the least incidence, a clear example is an investigation made by Chin *et al* in which the reported incidence was only 7% [9]. This can be explained by a better sensitivity for histopathological diagnosis and a greater rate of false positives in imaging techniques, as some other pathological mechanisms could resemble RN, including pseudoprogression, radiation-induced neoplasms, and vascular thrombotic events [10].

3. Pathophysiology of radiation necrosis

Vascular and white matter (myelinated tissue) injury have been stated as the genesis of RN. Since the second half of the 20th century, anecdotal clinical literature argued about the existence of delayed radiation-induced necrosis of the brain; however, scarce evidence was available regarding the exact mechanisms

of disease [11]. In the 1970s and 1980s, two main pathogenetic theories were formulated. The first one was the glial cell theory, in which radiation injury was presumed to induce damage of glial cells, specifically of oligodendrocytes, which will induce a cascade of events that will end in tissue necrosis [12]. The other theory stated that endothelial cell injury induced by radiation was the only cause explaining ischemia and further tissue necrosis. Different experimental studies performed in rats and dogs found data that supported both theories, and today we consider that RN arises as a multifactorial process in which glial cells, endothelial cells, and other cell types result injured by radiation generating different inflammatory and scarring processes that end in tissue necrosis [13–15].

Both theories are currently accepted as part of one single process in which vascular injury precedes glial cell damage. After brain tissue is exposed to radiation, avascular insult occurs within the first 24 hours, followed by parenchymal brain injury [16]. Reactive oxygen species develop because of ionizing radiation, leading to single- and double-stranded DNA damage. Regulatory cell mechanisms are activated and will drive the endothelium to cell cycle arrest and further apoptosis [17]. Ionizing radiation of more than 8 Gy will also induce activation of acid sphingomyelinase in endothelial cells [18, 19], leading to ceramide synthesis and ceramide-induced apoptosis [20]. The injured tissue will also induce inflammation, producing the release of TNF- α [21], a molecule that has been shown to disrupt the blood–brain barrier (BBB) in multiple physiological and pathological situations [22–24]. Increased expression of VEGF and ICAM-1 has also been shown [25, 26]. The result of this inflammatory cascades is the development of intravascular thrombi and fibrinoid necrosis, leading to vessel lumen narrowing and further ischemia and necrosis and disrupting, even more, the BBB homeostasis [27], leading to cerebral edema and further demyelination [28]. Thus, vascular injury induces oligodendrocyte injury, but at the same time, the initial ionizing radiation can also directly damage glial cells, generating inflammation and gliosis. In the early-delayed phase of this process, edema might resemble tumor progression or pseudoprogression on imaging findings [29]. Research has also shown that ischemia-induced hypoxia in the perilesional area can induce HIF- α , which also induces VEGF expression generating angiogenesis of weak, leaky capillaries that aggravate edema, necrosis, and demyelination. **Figure 1** shows the pathophysiological characteristics for the development of the RN.

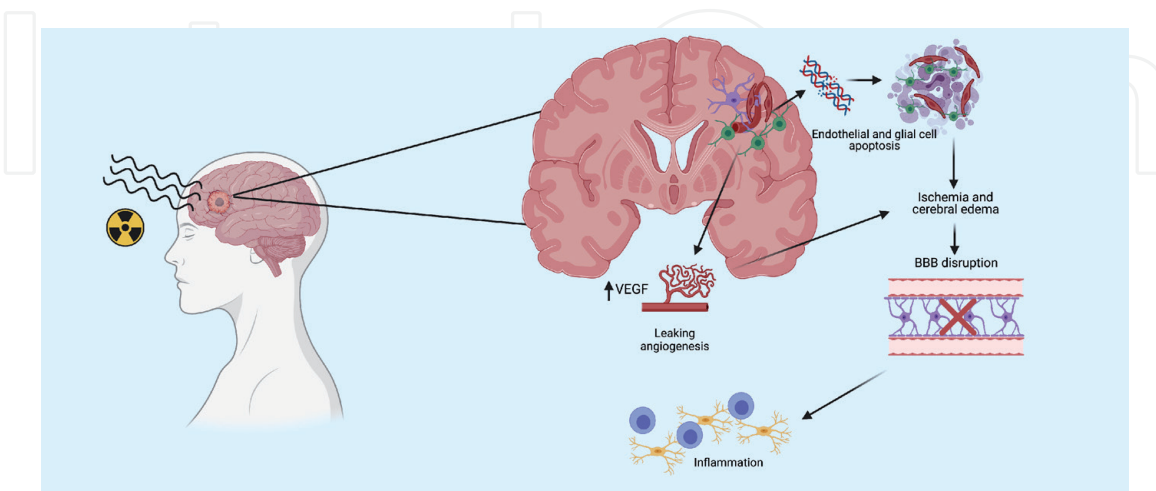


Figure 1.
 An illustration depicting RN pathophysiology is shown. When a patient receives radiation over a tumoral lesion, DNA damage occurs in glial and endothelial cells which will further lead to cell apoptosis. Vascular apoptosis leads to tissue ischemia and subsequent cerebral edema, processes that will facilitate BBB disruption with the further recruitment of inflammatory cells mediated by microglia. At the same time, increased expression of VEGF in response to hypoxia generates fragile neovessels that would leak plasma and would increase cerebral edema and BBB permeability.

4. Risk factors related to radiation necrosis

As a result of different epidemiological, clinical, and genomic studies related to radiation-associated brain injury, different risk factors for RN have been identified.

4.1 Dose-volume interplay

The incidence of RN increases as dose and volume increase. Different studies have tried to find the ideal dose for different tumor diameters. Lesions of 20 mm or less can be safely treated with 24 Gy, 21–30 mm lesions with 18 Gy, and lesions between 31–40 with 15 Gy. The cumulative incidence of RN at 12 months for these measurements is 8% [30]. In the case of SRS, it has been demonstrated that the brain parenchyma that is irradiated with >10–12 Gy has a greater risk of developing RN. This risk is even higher when $V_{10} > 10.5 \text{ cm}^3$ or $V_{12} > 7.9 \text{ cm}^3$ [8].

4.2 Prior radiation exposure

Another essential risk factor for RN is prior radiation exposure, whether as whole-brain radiation therapy (WBRT) or SRS. A study performed by Sneed *et al.* showed that the risk of developing RN after SRS in a patient with prior SRS in the same lesion was 20% at one year, 4% when WBRT was the primary modality, and 8% when concurrent WBRT. When no history of prior irradiation, the risk was only 3% [31]. Andruska *et al.* studied the incidence of symptomatic RN in 75 patients with brain metastases that received different doses in five fractions. With a median follow-up of 8 months, 14 patients were diagnosed with symptomatic RN; half of them were not previously exposed to brain radiation. However, in a subgroup analysis by dose received, patients with a history of prior intracranial irradiation only developed RN after 30 Gy, with the highest incidence when the dose was over 35 Gy [32].

4.3 Chemotherapy

Radiosensitization with cytotoxic agents is a common practice in the treatment of different tumors and metastatic diseases [33]. In the same study by Sneed *et al.*, the use of capecitabine +5-fluorouracil was related to a higher incidence of RN [31]. Ruben *et al.* studied 426 patients who underwent intracranial RT for glioma treatment; they found that patients who received subsequent chemotherapy significantly increased the risk of RN ($p = 0.001$) [34].

4.4 Immunotherapy

Colaco *et al.* studied 180 patients who underwent SRS for brain metastases. Only 39 developed RN from this cohort, from which only 35% received immunotherapy (IT) (the agents received were anti-CD137, anti-CTLA4, anti-PD-1, interferon, and interleukin-2), from these patients, 12 had IT only, and 2 received IT plus targeted therapy. In the multivariate analysis, patients who received IT only were at higher risk of developing RN; however, the difference was not statistically significant ($p = 0.06$). Statistical significance was evidenced in the univariate analysis ($p = 0.03$) [35]. Another study by Martin *et al.* included 480 patients that underwent SRS for BMs. They found that the receipt of IT was associated with symptomatic RN ($p = 0.04$), with the association being robust in melanoma patients ($p = 0.03$) and being even more substantial in melanoma patients receiving

Ipilimumab ($p = 0.01$). As it is widely known, checkpoint inhibitors are pro-inflammatory. Therefore, it is biologically plausible that its use can exacerbate the myriad of pathological mechanisms underlying RN [36].

4.5 Tyrosine-kinase inhibitors

Juloori *et al.* performed a study of 326 patients with 912 renal cell carcinoma with BM that underwent SRS. The cumulative incidence of RN at 12 months was 8%. It was found that the use of TKIs within 30 days from SRS was associated with a significantly increased 12-month cumulative incidence of RN (10.9% vs. 6.4%, $p = 0.04$) [37].

4.6 Brain location

Even though most studies did not find a correlation between brain location and RN risk, some observations by Flickinger *et al.* in arteriovenous malformations (AVMs) suggest that the frontal cortex is at higher risk of RN and that the brain-stem seems to be more resistant to radiation. Superficial lesions might also be at less risk of RN than the deeper ones [38].

4.7 Histology

Specific histological subtypes of tumors might be related to an increased risk of RN. Miller *et al.* at the Cleveland Clinic studied 1979 patients with metastatic lesions that received intracranial irradiation. From this pool, 15% of patients presented with RN. Analysis by histological subgroups revealed that HER2-amplified status ($p = 0.02$), BRAF V600E mutational status ($p = 0.04$), lung adenocarcinoma histology ($p = 0.02$) and ALK rearrangements presence ($p < 0.01$) were associated with a greater risk of RN [39].

4.8 Planning target volume (PTV) margin

A higher PTV might be related to an RN's increased risk. A study by Kirkpatrick *et al.* evaluated the risk of RN in 49 patients with 80 BMs. Patients were randomized to receive a 1 mm or 3 mm expansion of their gross tumor volume. Patients with the greater PTV (3 mm) had the highest risk of RN ($p = 0.1$); however, statistical significance was not reached as only six patients developed RN [40].

4.9 Intrinsic radiosensitivity

A possible genetic radiosensitivity might also underly some of the risk burdens of some patients that develop RN. One *in vitro* study evaluated the radiosensitivity of fibroblasts extracted from 5 patients with AVMs that did not develop RN compared to those extracted from 2 patients that developed RN. The researchers found an increased sensitivity in the fibroblasts from the patients that had RN [41]. A recent genome-wide association study from China found that the RN of the temporal lobe was related to the presence of a particular single-nucleotide polymorphism in the CEP128 gene promoter related to radionecrotic temporal lobe injury. CEP128 gene encodes the centrosomal protein 128 kDa, which interacts with multiple radiation-resistant genes and plays a crucial role in functional cilia. When this exact mutation is replicated in a glioblastoma cell line (U87), cell survival is considerably decreased under radiation.

5. Radiation necrosis imaging

The pathology of progressive brain RN primarily includes inflammation and angiogenesis in which cytokines, chemokines, and vascular endothelial growth factors are upregulated [12, 15, 42, 43]. Distinguishing between RN and tumor progression is somewhat challenging on conventional imaging. Besides, obtaining tissue samples is invasive even in stereotactic biopsies, although pathological diagnosis remains the gold standard. Moreover, needle biopsy poses a risk of misdiagnosis because RN is typically a heterogeneous lesion with coexisting radiation necrosis and tumor cells [44]. Currently, RN is diagnosed by relatively less-invasive radiological examinations that evaluate the whole lesion, compared with needle biopsy. Strategies can be divided into two categories, the use of conventional radiological imaging [computed tomography (CT) and magnetic resonance imaging (MRI)], and nuclear medicine studies [single photon emission CT (SPECT) and positron emission tomography (PET)] [45].

Brain RN may occur during therapy (acute injury), a few weeks to 3 months after therapy (early-delayed injury), or more than three months after treatment (late injury). After conventional radiotherapy, RN typically involves large areas of the brain and may not be amenable to surgery [46]. On the contrary, the injury secondary to radiosurgery tends to be restricted to the site of treatment and, consequently, may respond well to surgical resection [47]. Computed tomography was found to be unreliable in this regard quite early [46, 48, 49]. The most cited MRI features are necrotic foci, contrast enhancement, and perilesional edema [50, 51]; Changes are most evident in T2-weighted and fluid-attenuated inversion recovery sequences. Unfortunately, these features are commonly present with recurrent tumors as well. Some MRI features have been thought to suggest radiation necrosis in previous reports: contrast enhancement with ill-defined borders and little or no mass effect and a “Swiss cheese” or “soap bubble” pattern (“cut green pepper”). On the other hand, Dequesada *et al.* noted that gyriform lesions and edema with marginal or solid enhancement suggested at least some viable tumor, adding that a lesion quotient (LQ) (which is the ratio of the nodule on T2 sequence to the total enhancing area on T1 sequence) of >0.6 was suggestive of tumor recurrence, while an LQ of <0.3 favored radiation necrosis alone [52]. Other authors however found this feature to be only 8% sensitive.

Years ago, some suggested that advanced imaging modalities might prove to be more reliable than MRI in the differential diagnosis of tumor versus necrosis. Taylor *et al.* [53] found that magnetic resonance spectroscopy (MRS) reliably identified 5 of 7 patients with active tumor and 4 of 5 patients with radiation necrosis. Others have found that MRS reliably distinguished pure tumor from pure necrosis but that no values could distinguish mixed specimens [54, 55].

Almost two decades ago, Tsuyuguchi *et al.* found that methionine positron emission tomography had a sensitivity of 78% and a specificity of 100% for detecting recurrent tumor versus RN [56]. Subsequently, Belohlávek *et al.* found fluorodeoxyglucose PET to be insensitive but specific [57].

Since then, the use of MRS, MR perfusion, and PET has been consolidated as effective techniques to help increase diagnostic confidence. These techniques are discussed below.

5.1 MR perfusion

Viable tumor has intact vasculature and thus higher perfusion and blood volume than necrotic tissue. An increased relative cerebral blood volume (rCBV) based on dynamic susceptibility-weighted MRI has been used for differentiating tumor from necrosis [58]. Sugahara *et al.* prospectively studied 20 patients with

enhancing lesions after irradiation using gradient-echo dynamic susceptibility perfusion MRI and reported that a normalized rCBV value greater than 2.6 or less than 0.6 was always indicative of tumor recurrence and radiation necrosis, respectively [59]. Later, Hu *et al.* reported rCBV of <0.71 as 92% sensitivity and 100% specificity for radiation necrosis, while another suggested an rCBV cutoff of <2.1 (100% sensitivity and specificity) [58].

However, much of the published information is retrospective and inconsistent. Barajas *et al.* reported significant overlap in rCBV values and proposed using the percentage of signal-intensity recovery (PSR) [60]. Furthermore, rCBV values vary between machines, depend on the acquisition methods, and are confounded by signal-intensity pileup artifacts and susceptibility artifacts from blood and contrast pooling within the lesions. Intravoxel incoherent motion (IVIM) is another method that provides quantitative diffusion and perfusion measurements based on a diffusion-weighted imaging (DWI) MR acquisition. Compared with the combination of normalized CBV and ADC, adding IVIM to rCBV substantially improved the diagnostic accuracy for differentiating recurrent tumor and RN from 86% to 93% [61]. This data has been validated against gold standard histopathology [62].

5.2 MRS

MRS provides additional information on the metabolic composition within an area of tissue by comparing several metabolites' relative concentrations. Ando *et al.* retrospectively studied 20 patients and found that a 1.5 threshold of choline-to-creatine (Cho/Cr) ratio had a sensitivity of 64% (95% CI, 35–87%), and a specificity of 83% (95% CI, 36–100%) for the detection of glioma recurrence [63]. Traber *et al.* reported a series of 43 patients, with an increased choline peak (50% higher than contralateral tissue) which implies a sensitivity of 72% (95% CI, 53–86%), and a specificity of 82% (95% CI, 48–98%) to distinguish tumor from RN; however, not in all patients there was a histopathological verification [64].

Besides, Lichy *et al.* tested multivoxel spectroscopy in a cohort of 24 patients with recurrent tumor suspicion and found that a Cho/Cr threshold ratio of 2.0 had 87% sensitivity and 89% specificity for the detection of tumor recurrence in contrast to RN [65]. Furthermore, Plotkin *et al.* assessed prospectively 25 patients with suspected recurrent glioma versus radiation injury by single-voxel MRS at 3 Tesla. They reported that a combined diagnostic threshold of choline-to N-acetyl aspartate (NAA) of 1.17 and Cho/Cr of 1.11 resulted in 89% sensitivity and 83% specificity for differentiating tumor against radiotherapy-induced chronic changes [66].

Zeng *et al.* also explored the diagnostic effectiveness of MRS with DWI on the evaluation of recurrent contrast-enhancing areas at the site of treated gliomas. The authors found that the Cho/NAA (1.71) and Cho/Cr ratios were significantly higher in recurrent tumors than in regions of radiation injury, and ADC ratios were significantly higher in radiation injury regions than in recurrent tumors. The results showed that the sensitivity, specificity, and diagnostic accuracy were 94.1%, 100%, and 96.2%, respectively [67]. In contrast, an elevated lipid-lactate peak and generalized decrease in other metabolites supported radiation necrosis [68]. MRS is limited by voxel size, often requiring the lesion to be larger than 1 cm [3] and is also affected by sampling errors within heterogeneous tumors and the proximity to the skull base.

Recently, Chuang *et al.* presented the results of a systematic review that included 397 patients included in 13 studies designed to differentiate tumor recurrence versus radiotherapy changes. The pooled difference in means (2.18, 95% CI 0.85–3.50) indicated that the average rCBV in a contrast-enhancing lesion was significantly higher in tumor recurrence than radiation injury ($p = 0.001$). Based

on a fixed-effect model of analysis encompassing the six studies which used Cho / Cr ratios for evaluation, the pooled difference in means (0.77, 95% CI 0.57–0.98) of the average Cho/Cr ratio was significantly higher in tumor recurrence than in RN ($p = 0.001$). In the same direction, there was a significant difference in ratios of Cho to NAA between recurrent tumor and necrosis (1.02, 95% CI 0.03–2.00, $p = 0.044$) [69]. At least two additional integrative studies demonstrated that MRS alone has moderate diagnostic performance in differentiating glioma recurrence from radiation necrosis using metabolite ratios like Cho/Cr and Cho/NAA ratio [70, 71]. **Figure 2** shows the main imaging characteristics in conventional MRI (contrasted T1 phase), MR perfusion and MRS.

5.3 PET

Impaired BBB is considered the leading diagnostic indicator of brain tumors and metastases on contrast-enhanced MRI and CT. Similarly, many PET tracers that can identify tumor cells at various sites in the body would only reach the brain if the BBB is disrupted. Therefore, the development of specific tracers that do not depend on BBB damage, such as fluorodeoxyglucose (18F-FDG) and labeled amino acids (aa) that are transferred by specific transporters across the intact BBB was introduced. Different studies showed that 18F-FDG is unhelpful in differentiating tumor progression from RN. Even though 18F-FDG alone has a low sensitivity (43%), its combination with other imaging techniques like MRI might increase its diagnostic usefulness [72]. The fact that tumoral or highly inflamed tissue might have an increased uptake of amino acids [73], and the relatively low uptake of normal brain tissue would provide a considerable tissue contrast. Compared to 201Tl, 18F-FDG is more specific but less sensitive to detect tumor recurrence since the former, before its uptake through the Na⁺-K⁺ ATPase pump, has a non-specific accumulation due to BBB breakdown. The latter lacks sensitivity because of the physiological uptake

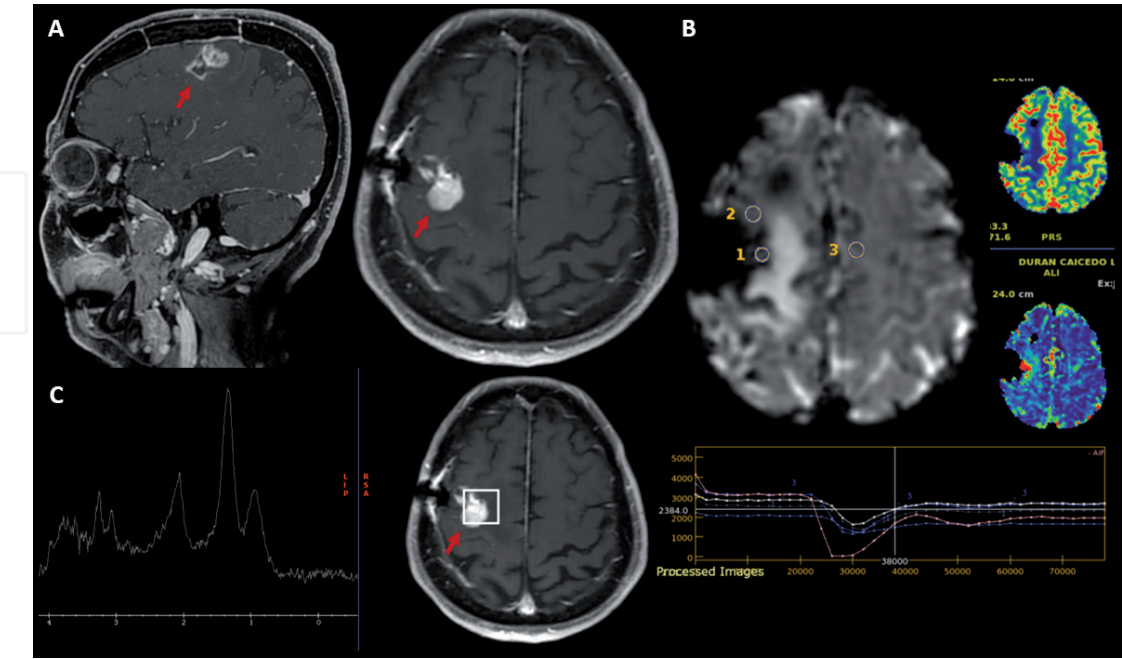


Figure 2. (A) Post-surgical right parietal changes due to resection of a metastatic lesion adjacent to the precentral sulcus with enhancement in the contrasted T1 sequence after SRS execution (compatible with RN). The lesion has an irregular morphology and measures 18x13x16.7 mm. (B) Decrease in all metabolites compared to the healthy zone, without evidence of Cho/NAA ratios greater than 2.0. There is also an increase in the peak of lactate-lipids, indicating that it corresponds to RN. (C) In the postsurgical cavity and in the nodular lesion that is enhanced with contrast medium, there are low values of rCBV.

of normal brain [74]. More specifically, in the differentiation of tumor recurrence and RN, 18F-FDG also has low specificity, ranging from 40 to 94%, mainly during the first few weeks post-therapy, with a study that showed a sensitivity of 81–86%. Therefore, it is recommended to perform 18F-FDG PET no less than 3 months after the end of RT, also because it can cause inflammatory changes that can last up to 6 months after therapy but slowly decreases over time, for example, in the lung parenchyma, which will take up FDG and make it difficult to differentiate from the recurrent tumor [75].

Other amino acids have been studied, including fluoro-1-thymidine, fluoro-ethyltyrosine (18F-FET), 3,4-Dihydroxy-6-18F-fluoro-1-phenylalanine (FDOPA), l-[Methyl-11C] methionine (11C-MET), 3-Deoxy-30-18F-fluorothymidine (18F-FLT) and carbon-11 choline. Floeth *et al.* compared 18F-FET performance with MRI and MR spectroscopy in 50 patients, showing in 34 tumoral lesions a mean tumor/non-tumor ratio (T/NT) of FET uptake of 2.4 ± 0.9 , thus significantly higher than non-neoplastic lesions (16 lesions; $p < 0.001$), with the area of significant 18F-FET uptake that was always included within the area of MR signal abnormality, which means that the latter could often be overestimating the extension of disease. More 30 out of 34 gliomas demonstrated an increased 18F-FET uptake (T/NT ratio > 1.6), with an overall sensitivity and specificity for the distinction of tumors from non-neoplastic tissues of 88% and 88%, respectively [76]. Concerning RN, studies have shown the absence of 18F-FET uptake in a case of RN in contrast to 18F-FDG; this could be due to the absence of 18F-FET uptake from macrophages, which are a common inflammatory mediator usually present in such cases. Recently, a study performed by Radinger *et al.* evaluated 36 patients with a glioma diagnosis. They used 18F-FET vs. MRS to differentiate tumor progression from RN correctly. In this study, pathological assessment and clinical manifestations were used as confirmatory variables. A specificity of 93% and a sensitivity of 100% was calculated for 18F-FET after suspicion of the recurrent tumor revealed by MRI (this highlights the importance of combining techniques for better analysis) [77].

18F-FDOPA is an amino acid tracer that has been used at the beginning for the evaluation of movement disorders by assessing the integrity of the striatal dopamine pathway. Recently, 18F-FDOPA is studied in the imaging of brain tumors. In this scenario, one of the main pros of 18F-FDOPA lays in the crossing of the BBB thanks to a specific neutral amino acid transporter, which grants a better uptake ratio also because tracer accumulation does not depend on BBB breakdown [78]. In a non-conventional meta-analysis, Yu *et al.* evaluated the accuracy of 18F-FDOPA and compared it to 18F-FET for differentiating RN from brain tumor recurrence going through 48 separate studies (18F-FDOPA, $n = 21$; 18F-FET, $n = 27$), in which both tracers showed comparable results in terms of pooled sensitivity (85%), specificity (82%) and diagnostic odds ratio (21.7); in particular, 18F-FDOPA showed better diagnostic accuracy in patients with glioma compared with patients with brain metastases and proved to be better than 18F-FET in diagnosing glioma recurrence. In any case, larger cohorts of patients will be needed to support these preliminary findings [79].

11C-MET is a PET amino acid isotope characterized by a relatively short half-life that in tumors determine the high density and activity of amino acid transporters. Instead, it can accumulate due to active transport and cell proliferation, but in RN, passive diffusion via BBB damage is the most probable uptake mechanism [80]. Therefore, the difference in terms of accumulation mechanisms could be a way to distinguish the two clinical settings. Concerning its role in the differentiation of recurrence from RN, Hustinx *et al.* explain the potential role of 11C-MET to differentiate either low-grade or high-grade gliomas. 11C-MET uptake was directly

related to prognosis and survival in low-grade gliomas since it is increased in the absence of BBB breakdown, thus determining a significant advantage over CT, MRI, or even 18F-FDG PET.

Moreover, in the case of high-grade gliomas, 11C-MET uptake is higher than in low-grade tumors; therefore, it could be used for monitoring purposes to assess anaplastic transformation [81]. In a recent study of 18 lesions from 15 patients with metastatic brain tumors who underwent gamma knife radiosurgery, the authors showed that 11C-MET was superior in terms of both sensitivity and specificity as an imaging technique for differentiating RN and recurrent metastatic tumors after gamma-knife compared with diffusion-weighted imaging (DWI), MR permeability imaging and 18F-FDG. However, it is not widely available yet for clinical use due to its physical limitations [82]. Another study showed that 11C-MET could differentiate recurrence from RN based on the PET/Gd volume ratio and the PET/Gd overlap ratio as these ratios were significantly lower in patients with RN than in patients with glioblastoma recurrence ($p < 0.05$) (analysis were done based on a pathological assessment) [83].

18F-FLT is a radiolabeled analog that has been used to indicate tumor proliferation since thymidine is a nucleoside encountered only in DNA; therefore, it reflects tissue proliferation rate. 18F-FLT transport is mediated mainly by active $\text{Na}^+ -$ dependent carriers through nucleoside transporters (salvage thymidine pathway) and passive diffusion. Enslow *et al.* made a tracer comparison taking in consideration 18F-FLT kinetic parameters (18F-FLT Kimax) rather than simple SUV max values [18F-FLT Kimax ≥ 0.0165 (sensitivity 91%, specificity 75%); 18F-FLT SUV max ≥ 1.34 (sensitivity 73%, specificity 75%)] and although there was no statistically significant difference both 18F-FDG and 18F-FLT proved to be accurate in the differentiation between recurrent glioma and radiation necrosis [84]. Unfortunately, even if dynamic kinetic modeling of 18F – FLT-PET has proven to be crucial and its superiority could not be demonstrated only for the small number of patients included in the study, due to the complexity of the procedure, it is unlikely that it will be broadly accepted in clinical practice. No single technique of PET and other imaging techniques has been shown to be able to differentiate recurrence from RN by itself. Based on the limitations of each modality, a multi-modal approach is currently used. **Figure 3** shows the differences between different PET tracers for the diagnosis of RN versus conventional MRI and the perfusion sequence.

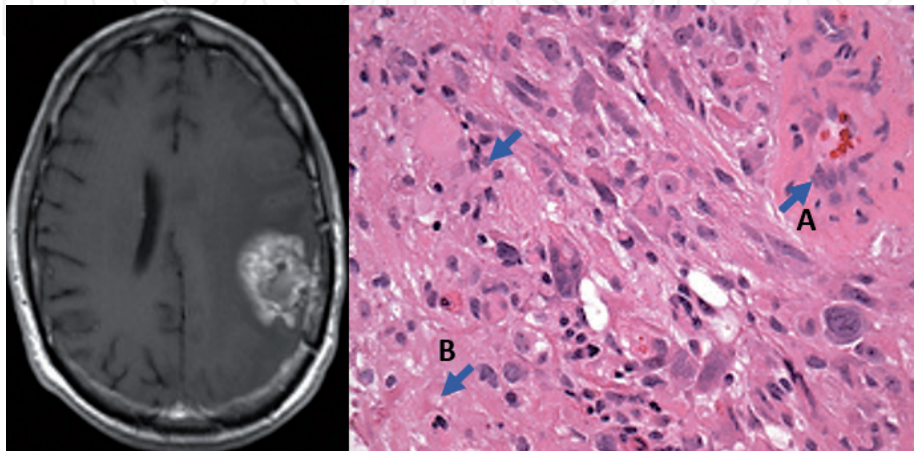


Figure 3.
A. Fibrinoid necrosis or hyalinization, fibrosis of blood vessels, dystrophic calcification and an inflammatory infiltrate consisting predominantly of macrophages. B. Radiation induced cytologic atypia.

6. Pathological assessment

Histopathology is currently the gold standard to diagnose tumor recurrence or RN. A significant difference in histologic findings exists between these two conditions. Macroscopically, RN shows as a firm-like mass or sometimes as a soft cystic lesion. A yellow-to-brown necrotic core is usually accompanied by significant hemorrhage, gliosis, and tissue atrophy [85]. In the case of RN, fibrinoid necrosis, hemorrhage, hyalinization and, blood vessel thrombosis can be seen, with a visible hypoxic injury of the surrounding tissue [5]. The necrotic area is usually paucicellular, characterized by the presence of inflammatory ghost cells and focal perivascular lymphocytes, and surrounded by gliotic brain tissue corresponding mainly to GFAP-reactive astrocytes (reactive gliosis) [86]. Inside the lesion, other cell types like foamy macrophages and hemosiderophages can be seen. A low nuclei-cytoplasmic ratio is characteristic. On the other hand, tumor recurrence shows a high cellularity with a

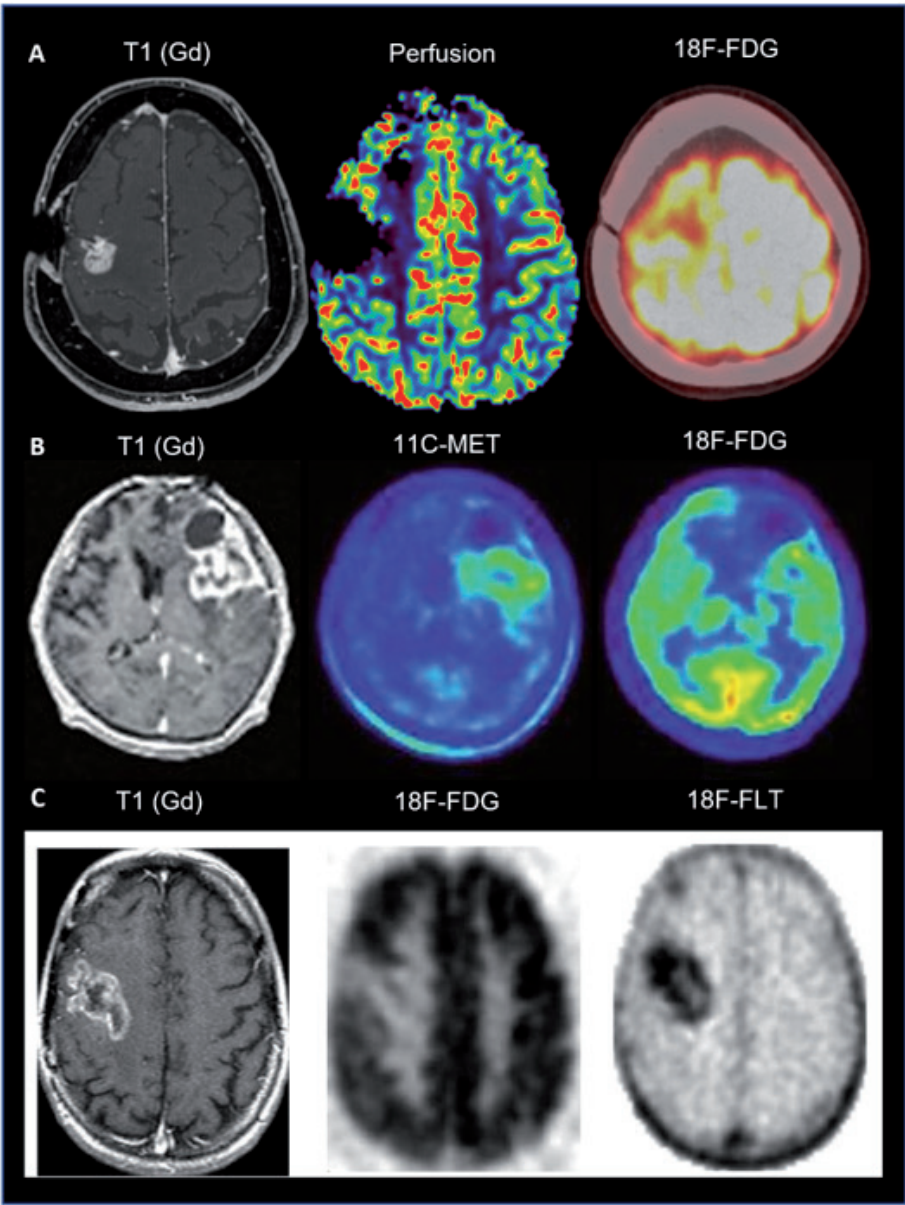


Figure 4.
Representative PET and MRI images of radiation necrosis (RN). (A) Example of an RN area by SRS performed in a postsurgical cavity due to metastasis of a lung adenocarcinoma located in the right precentral sulcus. (B) Variations between 11C-MET and 18F-FDG PET in a large area of left frontal RN after resecting a high-grade glioma treated with IMRT. (C) FLT-PET study from the progression of a recurrent glioblastoma multiforme. MRI T1 Gd shows a large right frontal contrast-enhancing lesion versus FLT- PET and FDG-PET scans.

ghost cell outline, demonstrating a high nuclei-cytoplasmic ratio. In brain metastases, careful examination of the blood vessels is essential as residual tumor cells might be seen around the Virchow Robin spaces. An immunohistochemistry panel will reveal the usual immunophenotype of the suspected tumor recurrence according to the patient's history. Histopathological assessment is not routinely performed unless an invasive approach to the lesions is needed for other purposes like therapeutic interventions. **Figure 4** shows the main pathological features of radiation injury, including cytological atypia, fibrinoid necrosis, and the marked inflammatory infiltrate.

7. Management of radiation necrosis

7.1 Observation

Since the 1970s, RN can be controlled with advanced images and left under observation. Wang *et al.* described a series of 124 patients who had radiation for nasopharyngeal carcinoma and developed severe imaging changes in the temporal lobe; among them, 28% of white matter lesions, 39% of contrast-enhanced lesions, and 7% of cysts regressed or resolved [87]. Since RN is not always symptomatic and evolutionary, it is considered that about half of the cases could be managed with observation, especially if the lesions are small and are located in non-eloquent areas.

7.2 Steroids

For patients with symptomatic brain RN, steroids are typically the first-line treatment, as they effectively reduce symptoms associated with brain edema and also inhibit the pro-inflammatory cascade involved in radiation injury. However, withdrawal of corticosteroids may result in a rebound of the edema and related symptoms and prolonged use of corticosteroids can be associated with significant toxicity including steroid myopathy, iatrogenic Cushing's syndrome and glucose intolerance [88].

7.3 Bevacizumab

There have been several recent reviews addressing the use of bevacizumab for brain RN [89, 90] that included data from both retrospective and prospective studies. Lubelski *et al.* reported on 30 patients included in seven studies of bevacizumab for patients with brain RN following treatment for high-grade glioma. Similar to this review, all patients demonstrated a radiographic response on T1 and T2-weighted MRI. Out of the 23 patients for which clinical data were reported, 16 (70%) showed an improvement. A subsequent broader review that included 71 patients treated with bevacizumab for brain RN after treatment of any brain tumor across 16 studies reported radiographic improvement in 97% of patients and improvement in performance status in 79% of patients [89]. Therefore, these reviews agree around information suggesting that the radiographic response rate to bevacizumab is high for patients with brain RN, and this response may be associated with symptomatic or functional improvement.

A recent systemic review found only three clinical trials with pharmacological interventions to reduce the clinical and radiological features of brain RN [91]. The first one is a randomized, double-blind, placebo-controlled trial of bevacizumab 7.5 mg/kg every three weeks for 2 cycles versus placebo tested in adults treated with radiotherapy for the brain or head and neck neoplasm and with radiological diagnosis of brain RN based on MRI criteria. Included patients were allowed to be taking corticosteroids before study participation, but they were required to be using a stable dose

for at least one week before receiving study treatment. The primary endpoint was the radiological response, defined as at least a 25% reduction in brain edema at six weeks of treatment compared with pre-treatment; this was measured as the volume of hyperintensity on T2-FLAIR MR images [92]. This trial reported that 100% (7/7) of participants on bevacizumab had a reduction in brain edema (T2 hyperintense volume) by at least 25% and a reduction in post-gadolinium enhancement.

In contrast, all those receiving placebo had clinical and/or radiological progression (five participants in the placebo arm experienced progressive clinical symptoms while two patients had radiological progression without progressive symptoms). Three severe adverse events were noted with bevacizumab which included aspiration pneumonia, pulmonary embolus, and superior sagittal sinus thrombosis [92].

The second was an open-label trial of patients treated with methylprednisolone 500 mg intravenously for three days followed by prednisone orally on a tapering schedule over 30 days, as tolerated, with or without the addition of edaravone 30 mg orally twice daily for 14 days. Eligible patients were adults (> 18 years old) treated with radiotherapy at least six months before study enrollment with radiographic evidence of RN based on MRI features. This trial also defined response as at least 25% reduction in the volume of T2-hyperintensity, and the primary endpoint was evaluated at three months following the start of treatment [93]. This study demonstrated a more significant reduction in brain edema in the edaravone plus corticosteroid group than in the corticosteroid alone group (mean difference was 3.03, 95%CI 0.14–5.92), although the result approached borderline significance ($p = 0.04$). There was no evidence of any critical difference in the reduction in post-gadolinium enhancement between arms (mean difference 0.47, 95% CI -0.80-1.74). Similarly, the participants who received the combination treatment were noted to have significantly greater clinical improvement than corticosteroids alone measured using the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT-SOMA) scale (OR 2.51, 95%CI 1.26–5.01). No differences in treatment toxicities were observed between arms, and no severe adverse events were reported.

Besides, one prospective non-randomized study allowed patients to choose between vitamin E 1000 IU twice daily for one year or no active treatment. Eligible cases were adults treated with radiotherapy for nasopharyngeal carcinoma with no evidence of recurrence for at least five years who have developed radiological evidence of unilateral or bilateral temporal lobe necrosis without mental impairment. Unlike the two randomized studies, serial imaging was not evaluated in this study. Patients were assessed at baseline and one year using a battery of in-house and more widely utilized neuropsychological tests, including the Cantonese version of the Mini-Mental Status Examination (CMMSE), Hong Kong List Learning Test (HKLLT), Visual Reproduction subtest of the Wechsler Memory Scale III (WMS-III VR), Category Fluency Test (CFT) and computerized Cognitive Flexibility Test [94]. Evaluating cognitive function in patients at baseline and after one year of treatment, a 5.3% improvement in global cognitive function on CMMSE was seen in patients who received vitamin E compared with no improvement in the control group ($P = 0.007$). Assessment of verbal learning using the Hong Kong List Learning Test (HKLLT) demonstrated that the treatment group had a 27.2% improvement at one year versus no improvement in the control group.

Similarly, improvements were seen for visual memory and recall for the group treated with vitamin E. There was no difference in attention, language, or executive function between the two groups at baseline or at one year. Corticosteroid requirements and adverse events to treatment were not reported in this study [94].

Another integrative study gathered the information from two prospective, seven retrospective, and three case report studies involving 89 patients with RN treated with bevacizumab [95]. In total, 93% of patients had a recorded radiographic

response to antiangiogenic therapy, and 6.7% had experienced RN progression. Seven studies ($n = 73$) reported mean volume reductions on gadolinium-enhanced T1 (mean 47%, ± 24) and T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI images (mean 62%, ± 23). Pooling together the T1 and T2 MRI reduction rates revealed a mean of 48 (95% CI 38–59) for T1 reduction rate and 62 (95% CI 52–72) for T2W imaging studies. Eighty-five patients presented with neurological symptoms at bevacizumab exposure, since when nine (10%) had stable symptoms, 39 (48%) had improved, and 34 (40%) patients had complete resolution of their clinical impairment. Similarly, dexamethasone discontinuation or reduction in dosage was observed in 97% of patients who had recorded dosage before and after bevacizumab treatment [95].

Considering the use of alternative ways for the administration of bevacizumab in patients with RN, Dashti *et al.* described two pediatric patients with cerebral arteriovenous malformations (AVM), who presented with medically intractable radiation injury following stereotactic radiosurgery. They received a single intraarterial infusion of 2.5 mg/kg bevacizumab after hyperosmotic BBB disruption. At a mean follow-up duration of 8.5 months, the patients had a significant and durable clinical and radiographic response. Both cases experienced resolution of their previously intractable headaches and reversal of cushingoid features as they were successfully weaned off steroids. One of the patients regained significant motor strength, and there was an associated greater than 70% reduction in cerebral edema [96].

Baroni *et al.* described pediatric patients' experience from five referral centers that treated 26 cases of symptomatic radiation necrosis with bevacizumab. The mean age at diagnosis of radiation necrosis was 10.7 years, with a median time between the last dose of radiation and the presentation of radiation necrosis of 3.8 months (range, 0.6–110 months). Overall, 50% of patients had an objective clinical improvement, with only one suffering from significant hypertension. Radiological benefit, defined as reduced T2/fluid-attenuated inversion recovery signal and mass effect, was observed in 50% of cases; however, this did not completely overlap with clinical response. Both early and late radiation necrosis responded equally well to bevacizumab therapy, and overall the monoclonal antibody was well tolerated, allowing the reduction of corticosteroid dose and/or duration [97].

7.4 Surgery

Although surgery is frequently used in clinical practice to address progressive resectable RN lesions, no prospective trials of surgical resection for brain RN were identified in this review. A retrospective series of 24 adult patients who underwent craniotomy and resection of contrast-enhancing lesions in the temporal lobes (16 unilateral and eight bilateral) following radiotherapy for nasopharyngeal carcinoma reported a reduction in the extent of brain edema observed on either CT or MRI (in those cases who had serial imaging). Only one patient required a repeat resection for recurrent necrosis [98]. In patients who were treated with radiosurgery, a retrospective series of 15 patients treated with surgical resection for RN reported improvement in brain edema resulting in either a partial or complete taper off corticosteroids as well as symptom improvement in the majority of patients [99].

7.5 Pentoxifylline and vitamin E

Pentoxifylline (PTX) is a methylxanthine derivative that decreases blood viscosity, increasing blood circulation and tissue oxygenation. Vitamin E (or tocopherol) acts as a free-radical scavenger. In a small retrospective study of 11 patients with

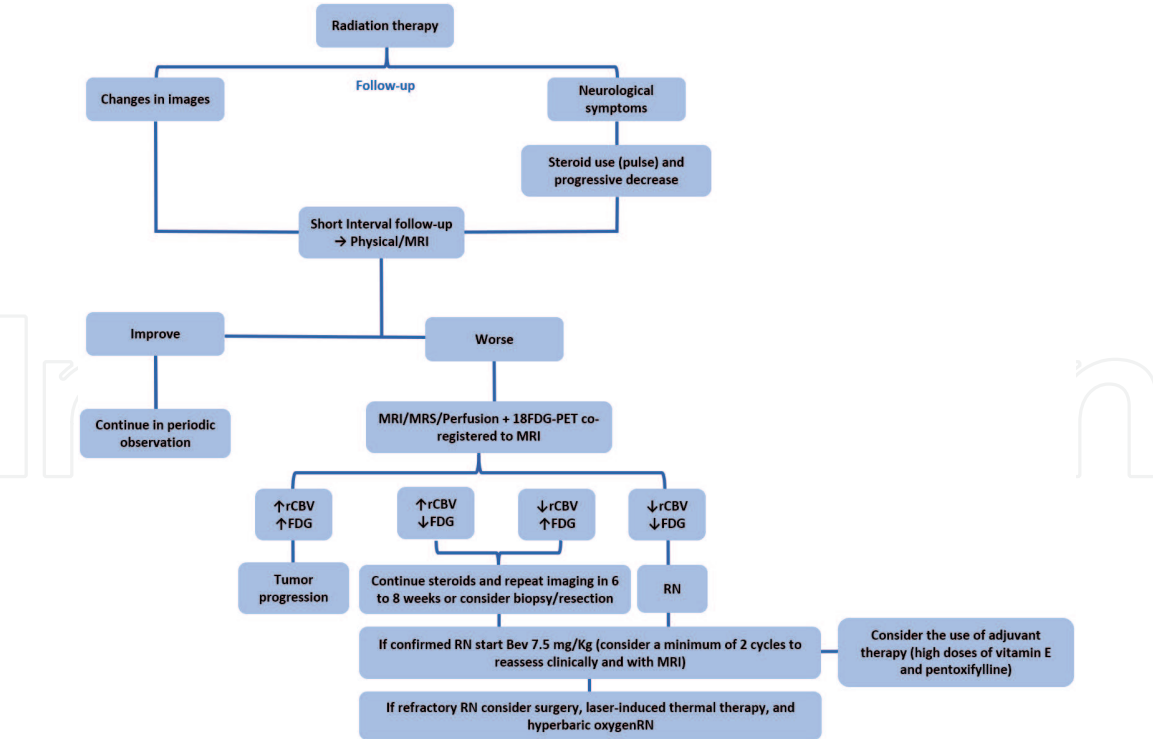


Figure 5.
Diagnostic and therapeutic algorithm for brain RN (modified from: Chao et al. [103]).

brain RN following radiotherapy for brain metastases, meningioma, and AVMs, the combination of PTX and vitamin E resulted in radiological improvement in all but one patient, who was eventually confirmed to have tumor recurrence [100].

7.6 Hyperbaric oxygen

There are limited small retrospective case reports and case studies reporting the outcomes of Hyperbaric oxygen (HBO) therapy for brain RN. Pasquier *et al.* reported limited retrospective reports of HBO as part of a more extensive review of HBO therapy for radiation injury to all body sites. These retrospective reports suggested favorable responses to HBO therapy to some patients; however, no prospective data is available [101]. Only one single-arm study evaluating HBO’s impact on clinical improvement and reduction of edema in patients who develop cerebral radiation necrosis following gamma knife radiosurgery (GKS) (NCT02714465) was on-going.

7.7 Laser-induced thermal therapy (LITT)

Only one single-arm study of a LITT reported promising local control of 75.8% (13 of 15 lesions) and dramatic reductions in lesion volume to less than 10% of the pre-treated volume in seven of the treated lesions [102]. However, as this was a single-arm study with a limited number of patients, a further prospective investigation is required to compare this treatment’s effectiveness against current management approaches. **Figure 5** shows a proposed algorithm for the diagnostic and therapeutic approach of NR.

8. Conclusions

Despite the rising incidence of RN because of increased utilization of stereotactic radiosurgery and reirradiation, there remain significant challenges in diagnosing

this complex brain injury. To date, there is no established standard to diagnose RN noninvasively. Over the past few years, there are, however, more treatment options, particularly with bevacizumab. More studies are needed to define who is at risk and how to minimize these risks; to diagnose radiation necrosis more accurately with imaging, blood tests, or other noninvasive techniques; and to treat these patients quickly before neurological signs and symptoms develop and progress.

Disclaimer

None.

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