

The management of brain necrosis as a result of SRS treatment for intra-cranial tumors

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Background: Stereotactic radiosurgery (SRS) is now a standard of care for recurrent malignant, metastatic and non-malignant brain tumors. Fortunately only a small number of tumors treated will result in asymptomatic or symptomatic necrosis. Radiographic determination of necrosis and then the implementation of treatment are important to alleviate new neurological symptoms. This article will review the identification and treatment for brain necrosis.

Methods: Although asymptomatic necrosis rarely needs treatment, brain necrosis resulting in neurologic change can be treated with steroids, surgery, bevacizumab and/or hyperbaric oxygen therapy.

Results: All the above methods have been used successfully in the treatment for SRS induced neurological complications from brain necrosis.

Conclusions: Corticosteroids, surgery, bevacizumab and HBO are all possible good treatment options for symptomatic RN. The treatment goal is to provide the patient with resolution of neurologic systems with the least toxicity and invasiveness.

Keywords: Brain necrosis/radionecrosis (RN); stereotactic radiosurgery (SRS); bevacizumab; hyperbaric oxygen therapy; steroids

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Introduction

Brain necrosis resulting from therapeutic irradiation to the whole brain, partial brain or stereotactic radiosurgery (SRS) is commonly referred to as radionecrosis (RN). RN is an infrequent yet well recognized SRS treatment risk for malignant, metastatic and certain benign tumors such as AVM's. The necrosis results from avascularization of the tissue at the site of the SRS target. The incidence of RN from SRS has been reported to occur in as many as 50% of treated metastatic lesions (1-6). Fortunately, most necrotic sites remain asymptomatic and heal with time over weeks to months. Factors which influence necrosis mainly include target dose and volume (7,8). Reducing either the dose or volume treated in order to avoid the RN risk has to be weighed against the importance of achieving high levels of

tumor over the patient expected life time. The symptoms of RN depend on the location and function of the brain at the injury site. These symptoms can range from headaches, fatigue, nausea, imbalance, extremity weakness/numbness, speech deficits, and seizures to a combination of the above.

Minniti *et al.* reported on the risk of SRS induced brain necrosis observed in 206 patients with 310 cerebral metastases (9). RN was radiographically documented in 24% of treated lesions with 10% of patients having new neurologic symptoms and 14% remaining asymptomatic. Median time to symptomatic necrosis was 11 months (range, 2-32 months). In their study, the development of RN was determined by MRI imaging. Volume and dose were independent risk factors for necrosis. The risk of necrosis was greater than 10% when the brain volume receiving the

12 Gy in a single fraction was greater than 8.5 cm³.

In our practice we have found that tumor growth versus SRS induced necrosis can be difficult to distinguish on a contrast enhanced brain MRI alone. Needless to say, the differentiation is important to recognize in an effort to provide appropriate patient management if new or worsening neurologic symptoms are present. If incorrectly diagnosed for tumor progression, SRS or whole brain irradiation retreatment could result in potentially larger areas of symptomatic necrosis. This article will review the current trends in identifying and managing patients that develops symptomatic SRS induced brain necrosis and conclude with a treatment algorithm guideline.

Radiographic differential for SRS brain necrosis

Despite the best efforts of the neuroradiology community, distinguishing SRS related brain necrosis from tumor recurrence and/or tumor progression as well as treatment related pseudo-response and pseudo-progression remains elusive (10-13). There is no single conclusive imaging methodology to distinguish between these processes. It is often the clinical course, a brain biopsy, or imaging over a lengthy follow-up interval that reveal recurrent tumor from radiation necrosis. The current imaging armamentarium available includes gadolinium enhanced MRI, MR Diffusion, MR Perfusion, MR Spectroscopy and PET-CT. Interpretation of these studies is aided by patient symptoms, tumor type and grade and treatment history including time course as well as the radiation dose and volume.

RN tends to occur at site of maximum radiation dose in the region of the tumor bed. Radiation disrupts the blood brain barrier (BBB) and its effect on blood vessels (occlusive vasculopathy) can potentiate ischemia (14,15). Analysis is further complicated by the fact that RN and viable tumor can coexist as a dynamic process and, although it is not always irreversible, may spontaneously regress and completely resolve. Also, anti-angiogenic (VEGF) drugs, such as bevacizumab, can normalize BBB permeability resulting in improvement of both tumors as well as RN.

MRI

Enhancement in a treated tumor bed occurs as a result of disruption of the BBB. This can be as a result of tumor recurrence other causes include post-surgical granulation tissue, ischemia, infection and RN. By conventional MR imaging it can be impossible to distinguish between

recurrent tumor and RN. Features pointing to RN include: (I) development of lesion away from primary tumor site; (II) development of multiple lesions; (III) lesion developing in the periventricular region as this area is prone to ischemia being in the end arteriole territory; (IV) lesion developing in a zone of atrophy and (V) lesion developing in the contralateral hemisphere. These features are useful in the case of a primary brain neoplasm but not so useful in metastatic disease (16).

RN may be suspected if: (I) an enhancing lesion develops in the bed of a previously non enhancing tumor; (II) there is development of lesion in an area of radiation induced leucoencephalopathy; (III) there is relatively little mass effect for size of the lesion; (IV) the lesion is peripherally enhancing with central necrosis. The enhancement may have an eccentric leading edge sometimes described as a “wavefront” (*Figure 1A*); (V) there is nodular enhancement in the zone of necrosis sometimes described as a “Swiss Cheese” enhancement (*Figure 1A*); (VI) there is associated hemosiderin and calcifications (*Figure 1B*); (VII) involvement of the corpus callosum and (VIII) dilatation of adjacent perivascular spaces is present (*Figure 2*) (17). Also see example in *Figure 2A-C*.

MR diffusion

Diffusion-weighted imaging (DWI) is based on the detection of a change in the random or Brownian motion of protons in cellular and interstitial water. When the diffusion of water molecules is diminished this is called “restricted” and when increased it is called “facilitated”. This “diffusability” can be measured on apparent diffusion coefficient (ADC) maps and enables characterization of disease processes. Acute infarct is typically characterized by restricted diffusion. Certain tumors such as epidermoids demonstrate marked restricted diffusion and this feature is vital in making the diagnosis. Tumors that are highly cellular such as lymphoma and meningioma can also have restricted diffusion.

There is overlap in the DWI appearance of RN and recurrent tumor. Occlusive vasculopathy as a result of radiation can result in ischemic change, with restricted diffusion and low ADC values (*Figure 3*). In the chronic stage there is a trend towards higher ADC values (facilitated diffusion) with RN (18). Other investigators using diffusion tensor imaging (DTI) have demonstrated the opposite higher ADC values in recurrent tumor as opposed to cases of RN (19).

MR perfusion

Dynamic susceptibility-weighted contrast-enhanced

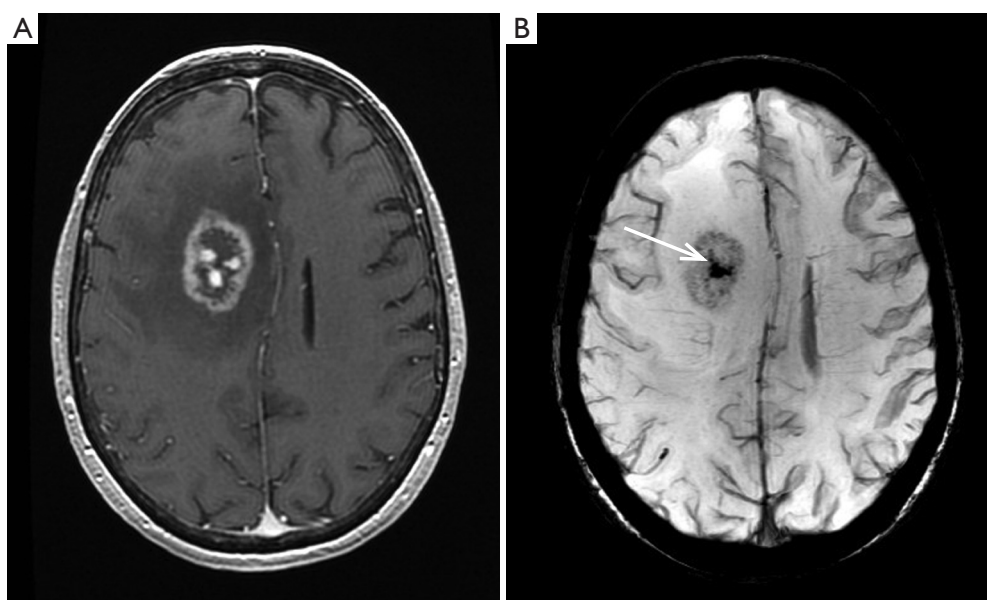


Figure 1 (A) T1 weighted post gadolinium scan demonstrating a clinically proven focus of radiation necrosis in the right frontal lobe in a patient with breast cancer. Note the location adjacent to the ventricle. This lesion demonstrates eccentric or “wavefront” and central nodular or “Swiss cheese” patterns of enhancement associated with radiation necrosis; (B) susceptibility weighted image (SWI) in the same patient demonstrates coarse central focus of low signal intensity. This is a typical finding in lesions treated with radiation (arrow).

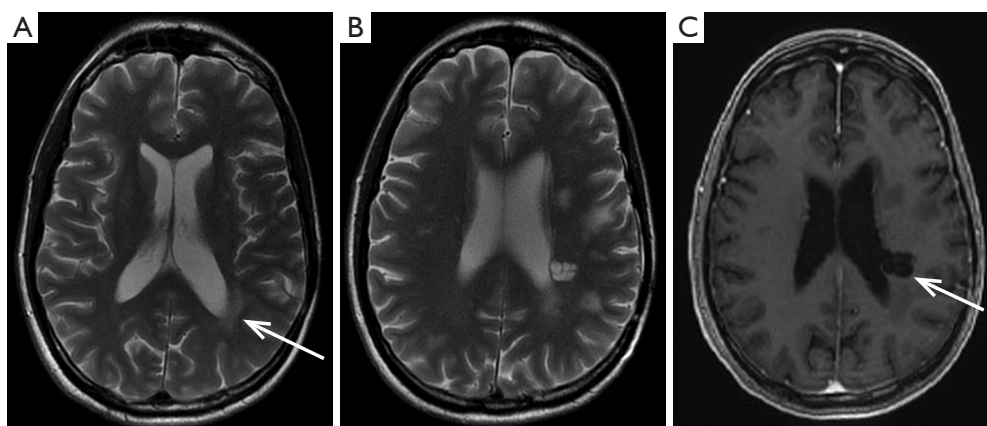


Figure 2 (A) Arrow demonstrating increased signal adjacent to the atrium of the left lateral ventricle corresponding to an area of radiation induced periventricular radiation leukoencephalopathy in a patient with treated breast cancer metastases; (B) same patient four years later, developing cystic spaces in the area of radiation leukoencephalopathy; Cysts follow CSF signal on all pulse sequences and are felt to represent dilated Virchow Robin spaces as a result of traction phenomenon from radiation induced scarring; (C) post gadolinium scan shows no enhancement (arrow) thus excluding tumor recurrence. Note the absence of mass effect for the size of the lesion.

perfusion MR imaging can estimate tissue microvascular density by measuring relative cerebral blood volume (rCBV). Radiation necrosis typically results in endothelial cell damage and small-vessel injury, resulting in decreased tissue perfusion. In contrast, tumor recurrence promotes angiogenesis and microvascular proliferation, helping to sustain tumor growth.

Measurements are obtained in the region of the putative area of necrosis/recurrent tumor and compared to normal tissue in the contralateral hemisphere resulting in a ratio (rCBV). rCBV >1.5 is indicative of recurrent tumor, rCBV <0.7 is indicative of RN (Figure 4A-C). Dynamic contrast enhanced (DCE) imaging with calculation of tissue permeability (K

trans) provides similar results but with the added advantage of diminished susceptibility artefact and higher spatial resolution (20-22) (Figure 5A-C).

MR spectroscopy

The resonant frequency of protons is altered by their chemical environment. This forms the basis for MR spectroscopy. The spectra typically displayed are expressed in units of parts per million (ppm). Commonly encountered

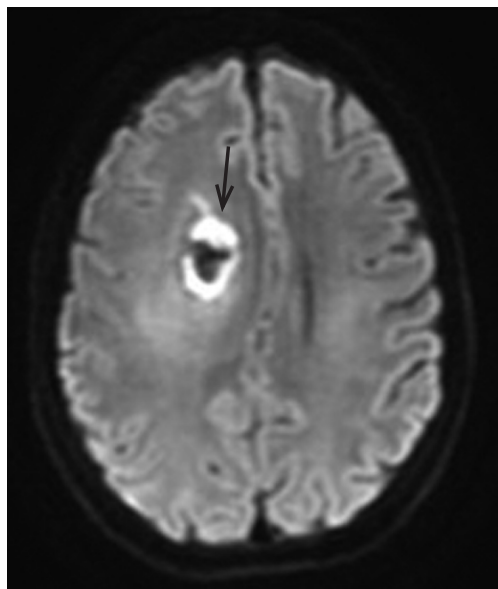


Figure 3 Diffusion weighted image (DWI) demonstrating a ring like area of restricted diffusion in an area of radiation necrosis, indicating ischemia (arrow).

metabolites in normal brain tissue include N-acetyl aspartate (NAA), choline and creatine. Lactate and lipids can also be detected.

NAA (2.0 ppm) is the largest peak in normal spectra. It is considered a marker of normal neuronal function. A decrease in NAA indicates axonal injury or neuronal loss. Choline is a component of the cell membrane. An increase in the choline peak (3.2 ppm) reflects an increase in membrane synthesis and increased cellular turnover/proliferation. Creatine (3.0 ppm) serves as a marker of the energy reserves in the cell and remains relatively stable even when disease is encountered. The lactate peak (1.32 ppm) consists of two distinct resonant peaks (a doublet), its presence indicates anaerobic metabolism (23).

Cho/NAA and Cho/Cr ratios tend to be significantly higher in recurrent tumor than in RN, whereas the NAA/Cr ratios are lower in recurrent tumor than in radiation injury (Figure 6A-C). Lipids are seen with necrosis and can be seen in tumors. Radiation sensitivity, specificity, and diagnostic accuracy of 3D 1H-MR spectroscopy for diagnosing recurrent tumor were 94.1%, 100%, and 96.2%, respectively, based on the cutoff values of 1.71 for Cho/Cr or 1.71 for Cho/NAA (23).

PET CT

Glucose metabolism can be measured by the uptake of [18F] FDG. Uptake is measured relative to cortex. Tumor cells generally have high rates of glucose metabolism, and therefore demonstrate high FDG uptake. Conversely, RN will have lower glucose metabolism and therefore low FDG uptake (Figure 7A,B). Low grade gliomas may have lower metabolism when compared to cortex. FDG PET may be less sensitive

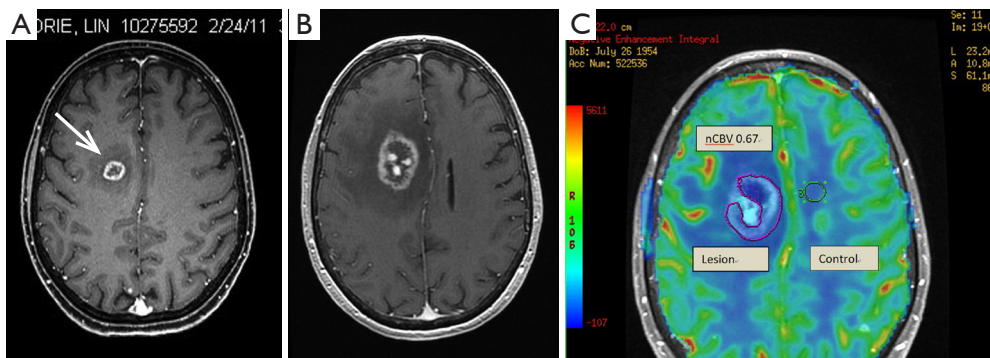


Figure 4 (A) Metastasis from breast cancer (arrow); (B) nine months following radiation the metastatic focus increased in size; (C) perfusion map demonstrates a low nCBV of 0.67 (nCBV =normalized cerebral blood volume) in the lesion compared to control. A nCBV value <0.7 suggests radiation necrosis and >1.5 suggests recurrent tumor. This supports the diagnosis of radiation necrosis as opposed to tumor progression.

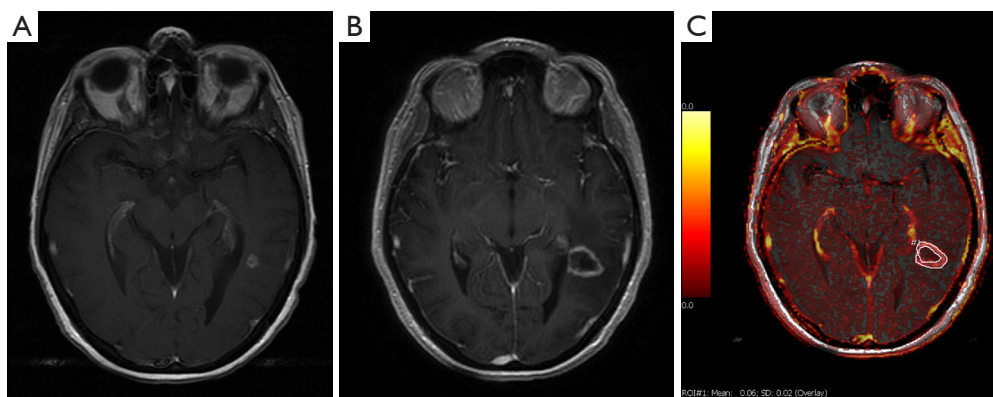


Figure 5 (A) Left temporal metastatic focus; (B) following radiation, the lesion increased in size with central necrosis; (C) dynamic contrast enhancement (DCE) map with demonstrates a low kTrans value of 0.06. kTrans is a measure of leakiness of the blood brain barrier (BBB) and is elevated in tumors. At our institution kTrans value of >10 is considered more likely to represent recurrent tumor. The low kTrans value in this case supports radiation necrosis.

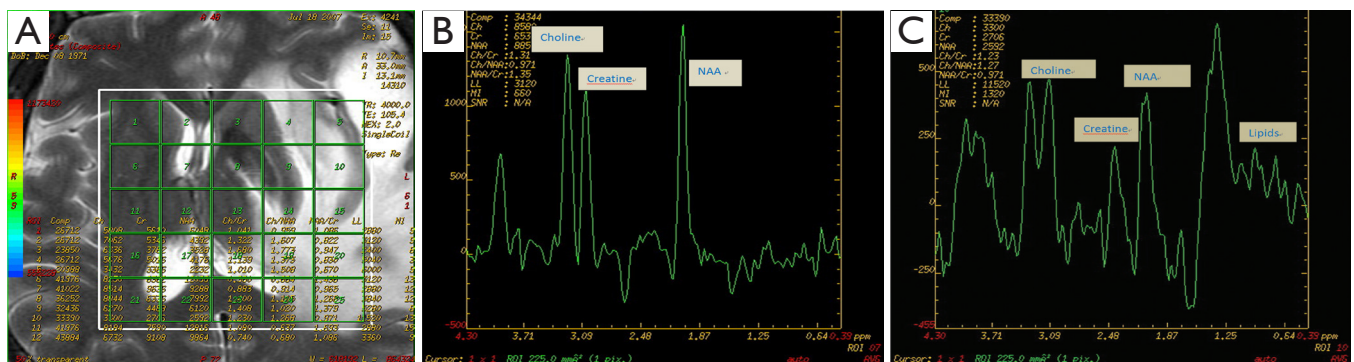


Figure 6 (A) 3D MR Spectroscopy. Patient with extensive edema in the left fronto-parietal region following radiation therapy. A grid is placed over the region of interest and spectra obtained from each individual voxel. There are 25 voxels in this grid; (B) MR spectroscopy from voxel No.1 (Control). Normal relationship of choline, creatine and NAA (N acetyl aspartate); (C) MR spectroscopy from voxel 10 (Lesion) demonstrating low levels of choline, creatine and NAA. This is typical for radiation necrosis. The presence of lipids indicates cell membrane breakdown further supportive of radiation necrosis.

in differentiating recurrence from radiation injury in these tumors. FDG PET can be false positive due to volume averaging with the cortex and seizure activity or false negative due to a mixture of a large percentage of necrosis with limited tumor. Imaging in the first three months following radiation or surgery may result in false-positive scans caused by increased metabolic activity arising from the healing process.

Evaluation is limited by low spatial resolution and beam hardening artefact from the skull base that makes it difficult to evaluate lesions in the temporal lobes, cerebellum and brain stem. In a study by Ricci *et al.*, PET findings were confirmed histologically in 31 patients. With contralateral white matter as the standard of comparison, the PET scan

sensitivity and specificity were found to be 86% and 22%, respectively. With contralateral gray matter as the reference standard, the sensitivity and specificity became 73% and 56%, respectively. Overall, nearly one third of the patients would have been treated inappropriately in either scheme had the PET scan been the sole determinant of therapy. They conclude that ability of FDG PET to differentiate recurrent tumor from radiation necrosis is limited (24).

Imaging preference at our medical center

After SRS treatment for brain metastases, patients are usually followed on an every 2-3 months bases with serial

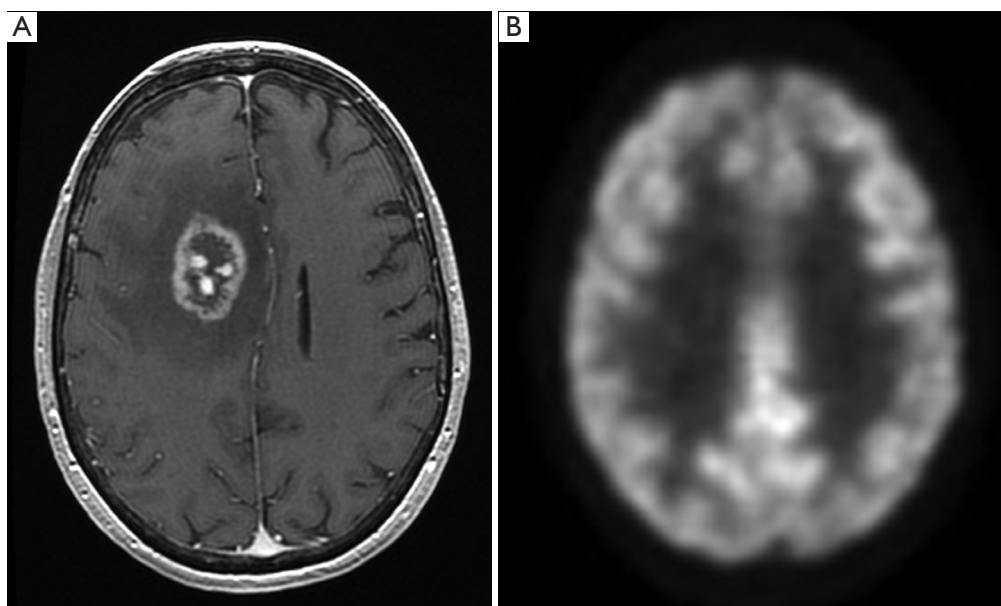


Figure 7 (A) Post gadolinium T1 weighted image demonstrate. an enlarging lesion in the right frontal lobe in a patient who has undergone radiation therapy for metastatic breast cancer; (B) [18F] DG PET CT. No evidence for glucose uptake at the site of the right frontal lobe lesion. This is supportive of radiation necrosis over tumor.

contrasted enhanced MRI scans which include perfusion and diffusion. If the patient's clinical findings and MRI suggests probable symptomatic RN and treatment intervention other than steroids is warranted, spectroscopy or a PET CT will be obtained for corroboration of necrosis. Spectroscopy is preferred because of its sensitivity over PET CT but is seldom covered by insurance.

Corticosteroid use in the management of brain necrosis

For patients who present with radiographic changes on MRI and symptoms suggestive of necrosis, the mainstay of treatment is corticosteroids until the lesion heals or symptoms resolve. During this time, in order to avoid the long-term effect of corticosteroids, the dose should be the lowest possible to reduce the edema. Unfortunately, even with small doses, not all patients tolerate the sometimes immediate effects of corticosteroids which include anxiety, sleeplessness, aggressive behavior, depression, GI irritation, increased appetite and swelling of the hands, feet and face.

Bevacizumab in the management of SRS brain necrosis

Evidence has implicated the upregulation of VEGF in the

pathogenesis of radiation induced brain necrosis making it an attractive therapeutic target (25,26). Bevacizumab, a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), is an anti-angiogenic therapy with the best-supported evidence in patients with symptomatic RN who respond poorly to corticosteroids as initial symptomatic management (27-30). Pharmacologic blockage of VEGF with bevacizumab can restore BBB function and markedly reduce cerebral edema and mass effect with subsequent improvement in neurologic symptoms (27).

Gonzalez *et al.* retrospectively reviewed 8 patients with RN treated with bevacizumab and reported a mean reduction in T1-weighted post-gadolinium abnormalities of 48% and a reduction in the fluid-attenuated inversion-recovery (FLAIR) abnormalities of 60% (27). A significant reduction in steroid requirement by 8.6 mg daily was also observed. Subsequently, a double-blind, placebo-controlled trial conducted by Levin *et al.* evaluated 14 patients with radiographic or biopsy confirmed RN, randomized to receive bevacizumab 7.5 mg/kg or intravenous saline at 3-week intervals for four treatments (28). All bevacizumab treated patients (five of five randomized and seven of seven crossover), and none of the placebo-treated patients, demonstrated a decrease in FLAIR and T1 post-gadolinium abnormalities as well as improvement in neurologic

symptoms. At median follow-up of ten months after four doses of bevacizumab, only two patients experienced a recurrence of radiographic changes consistent with progressive RN for which bevacizumab was resumed for one to two doses. This study demonstrated the efficacy of bevacizumab in the treatment of cerebral RN and was later confirmed in a retrospective review published by Sadraei *et al.* (29). Twenty-three of 24 patients with RN treated with varied dosing regimens of bevacizumab demonstrated radiographic improvement with mean reduction in T1-weighted post-gadolinium abnormality of 48.1% and average reduction in FLAIR abnormalities of 53.7%. They additionally reported a daily dose reduction of dexamethasone by 9.4 mg after the initiation of bevacizumab. Therapy was well tolerated with one grade three adverse event. Boothe *et al.* additionally retrospectively reviewed a series of 11 patients treated with bevacizumab for SRS induce brain necrosis (30). The mean percentage decrease in post-gadolinium and FLAIR volume was 64.4% and 64.3% respectively, with reduction in steroid requirements and all but one patient demonstrated improvement or stability of neurologic symptoms.

Questions remain regarding the ideal dosing and treatment duration for bevacizumab in RN, without an observed difference in clinical and radiographic outcomes. Bevacizumab is most commonly administered at 10 mg/kg every two weeks or 7.5 mg/kg every three weeks. Based on the only randomized, double-blind, placebo-controlled trial and retrospective analyses, it is reasonable to administer bevacizumab for approximately 4 doses followed by a period of observation with surveillance MRI every six to eight weeks. In the event of recurrent RN, this may be resumed for a short duration.

Bevacizumab to date is the best-supported therapy for radiation induced brain necrosis and should be considered in patients with progressive neurologic symptoms refractory to more conservative therapies. Bevacizumab offers symptomatic relief, reduction in steroid requirements and dramatic radiographic response and may obviate the need for surgery. Due to potential toxicities including hypertension (4-16%), proteinuria (0-3.2%), wound healing complications (0-2.4%) and vascular events such as intracranial hemorrhage (all grades/>grade 3, 0-3%/0%) and venous thromboembolism (2.0-12.6%), careful selection of patients should be made prior to initiating treatment (31). Contra-indications to bevacizumab include patients with intracerebral hemorrhage and in patients with metastases at

high risk for hemorrhage such as melanoma.

Surgical management of SRS brain necrosis

RN often presents as a mass producing lesion necessitating surgical removal. When corticosteroid and anti-angiogenic strategies are incapable of eradicating an edema-generating lesion causing mass effect in the setting of neurological deterioration, surgical removal must be considered. The neurosurgical approach to such lesions is no different than that of a primary tumor. The goal is to resect necrotic tumor and brain tissue that serves as an edema-generator. Standard neuronavigation and microsurgical techniques are utilized to resect enhancing areas of necrotic tumor and brain tissue. Under the operating microscope, areas of radiation necrosis often appear as leathery scar-like areas adjacent to edematous white matter. Careful resection of enhancing lesional tissue often provides significant reversal of the edema-producing effects of the areas of RN, and patients may be able to be weaned from corticosteroids. Many patients will have significant improvements in neurological function. Most operations to resect areas of RN in the brain result in similar outcomes as with a tumor resection in terms of postoperative morbidity and hospital stay.

If the tumor is not surgical assessable without significant morbidity and diagnostic scan are equivocal for necrosis, a biopsy may be warranted to rule out active disease. Since there is an increased risk of surgical wound dehiscence associated with bevacizumab, at our institution we delay surgery 4-6 weeks after the last administration of the drug.

Hyperbaric oxygen therapy in the management of brain necrosis

It has been estimated that one-third of cancer patients in the United states receive hyperbaric oxygen (HBO) for radiation induced injury (32). Normal tissue injury by radiation includes vascular damage, stromal fibrosis and the depletion of parenchymal as well as stem cells. Hyperbaric oxygen therapy has been shown to enhance angiogenesis in hypoxic or necrotic tissue, reduce fibrosis and mobilize stem cells within the irradiated tissue (33-37). HBO enhances the amount of dissolved oxygen in the plasma and thereby delivering more oxygen to the surrounding tissue. At a pressure of 3 atmospheres (304 kPa), dissolved oxygen approaches 60 mL/L of plasma whereas the sea-level concentration is only 3 mL/L. This difference in oxygen increase is sufficient to supply the resting tissue's need

without the contribution from oxygen bound hemoglobin. Therapeutic treatment pressures used inside a chamber are increased to 250-280 kPa. These pressures are equivalent to that experience in an underwater depth of 15-18 meters or 45-48 feet of water. Compared to monoplace chambers, the multiplace chambers are less claustrophobic and have less fire-risk since the high oxygen pressure is only released into the tight fitting patient mask and not the room itself. The multi-place chambers also have less risk of cross infection and assistants can enter the chamber if a patient problem should arise. The duration of a daily treatment is typically less than 120 minutes but can vary from 45-300 min. A typical treatment course is 20 sessions. However, courses may be repeated depending on the patient's response. For RN injuries, three consecutive courses for a total of 60 sessions have been given in our patient population.

Side effects of hyperbaric oxygen are often mild and reversible. Severe life threatening side effects are rare. Severe central nervous system symptoms including seizures occur in 1-2%, symptomatic reversible barotrauma in 15-20%, pulmonary symptoms in 15-20% and reversible myopia in 20% of patients treated (38). Myopia is the most common side effect due to the oxygen toxicity to the lens and, although reversible, can last for weeks to months.

In the largest series to date using HBO for RN, Gesell and her colleagues reported on the outcome in 29 patients (39). Objective neurologic exam improvement was observed in 58% of these patients while the need for steroids was reduced 69%. Other authors have seen similar results with a reduction of the size of necrosis on subsequent imaging studies for both SRS treated malignant tumors and AVMs (40-42). All in all, 65 patients in combined reports resulted in a 68% neurologic improvement following HBO for brain parenchyma radiation induced injury.

Although there is an expressed concern regarding reactivation of dormant malignant cells following HBO, there has been no observable recurrence documented in any of the literature (32,43). Although concern is warranted, the numbers are expected to be small.

Systematic reviews on HBO and cancer have concluded that the use of HBO in patients with malignancies is an option for corticosteroid refractory RN particularly if surgery is not an option to remove the lesion.

A proposed guideline for the treatment of brain necrosis from SRS

In summary, corticosteroids, surgery, bevacizumab

and HBO are all possible good treatment options for symptomatic RN. The option selected should provide the patient with resolution of neurologic systems with the least toxicity and invasiveness. A suggested treatment guideline we use at our institution is as follows:

- (I) Patients who have received SRS for brain metastases are followed with serial MRI scans every 2-3 months to assess disease response to radiation treatment and to rule out the interim development of new metastases. All brain MRI scans are obtained with and without contrast and include perfusion/diffusion.
- (II) If the MRI scan reveals a probable necrotic lesion and the patient is asymptomatic, observation alone is advised with a repeat scan at 2-3 months intervals.
- (III) If the MRI scan reveals probable RN and the patient is symptomatic, the lowest dose of corticosteroids (i.e., dexamethasone) can be offered for control of neurological symptoms. If the corticosteroids are tolerated, they can be continued until the lesion heals. If corticosteroids are not tolerated and the neurological symptoms from edema continue other treatment interventions should be considered.
- (IV) Patients who become refractory or intolerant to corticosteroids are discussed at tumor board. The prior radiation course, timing of new neurologic symptoms and changes on the MRI scan are review. Spectroscopy or a brain PET CT maybe obtained. If both sets of imaging are equivocal and the lesion is assessable, surgical resection can be offered to remove the mass. If removing the mass subjects the patient to unreasonable surgical risks, a biopsy might be attempted. The purpose of the biopsy is to distinguish between RN *vs.* active tumor so the appropriate treatment can be administered.
- (V) If the patient is not eligible for surgery or the lesion does not cause significant mass effect, bevacizumab or hyperbaric oxygen therapy can be offered. If one therapy is not effective the other can be tried.

Fortunately, symptomatic RN is rare and many treatment options exist. Indeed, all the methods discussed in this article we have found effective in the treatment of SRS induced brain necrosis.

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