Critical Review

Challenges With the Diagnosis and Treatment of Cerebral Radiation Necrosis

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Received Mar 6, 2013, and in revised form May 2, 2013. Accepted for publication May 5, 2013

The incidence of radiation necrosis has increased secondary to greater use of combined modality therapy for brain tumors and stereotactic radiosurgery. Given that its characteristics on standard imaging are no different that tumor recurrence, it is difficult to diagnose without use of more sophisticated imaging and nuclear medicine scans, although the accuracy of such scans is controversial. Historically, treatment had been limited to steroids, hyperbaric oxygen, anticoagulants, and surgical resection. A recent prospective randomized study has confirmed the efficacy of bevacizumab in treating radiation necrosis. Novel therapies include using focused interstitial laser thermal therapy. This article will review the diagnosis and treatment of radiation necrosis. © 2013 Elsevier Inc.

Introduction

Radiation necrosis is a late complication of radiation to the brain or surrounding structures. Although this had been relatively uncommon, the incidence is increasing with greater utilization of stereotactic radiosurgery (SRS) and combined modality therapy for brain tumors. Patients can develop symptoms from radiation necrosis that infrequently can be a cause of death. Despite numerous modalities to image the brain, ranging from structural scans such as magnetic resonance imaging (MRI) and computed tomography (CT), and metabolic scans such as magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission CT (SPECT), these techniques are imperfect and accurate diagnosis of radiation necrosis remains difficult. There are numerous treatment modalities for radiation necrosis, with bevacizumab being the most proven of these. The history, pathophysiology, diagnostic modalities, and treatment techniques of radiation necrosis will be reviewed.

History

Cerebral radiation necrosis was first described by Fischer and Holfelder in 1930 after radiation of the scalp to a dose of 6840 cGy in a 45-year-old gentleman (1). Despite knowledge of radiation necrosis, it took 5 decades to properly define this complication. Sheline et al (2) developed a classification scheme based on the temporal relationship to radiation treatments, which is summarized in Table 1. One form of early delayed injury is pseudoprogression and should always be considered in the first 3 months after concurrent chemoradiation for gliomas (3). Other forms of early delayed injury include somnolence syndrome seen in pediatric patients and L’Hermitte syndrome seen in the spinal cord.

Conflict of interest: M.A. is a consultant for Elekta, Novocure, Genentech, and Monteris and is on the speakers bureau for Merck and Sigma Tau. G.B. is a consultant for Monteris. G.S. is on the speakers bureau for UCB. J.S. is a consultant for Abbott.
cord (4). On the other end of the spectrum, radiation necrosis is part of late injury that occurs a few months to years after treatment. This is largely irreversible and may be characterized by a focal pattern demonstrating a circumscribed lesion, possibly with edema. In this article, radiation injury will be defined as being reversible and radiation necrosis being irreversible (permanent radiation injury).

Brain tumors have been an ideal target for stereotactic radiosurgery given the ability to immobilize the cranium, allowing for high doses with sharp falloff to be delivered to brain tumors. Although initially developed in the 1950s, the development of SRS followed the development of CT and MRI in the 1980s, allowing radiation oncologists and neurosurgeons to target tumors visible on imaging. In the 1990s, trials for SRS were being conducted with a concern that SRS would result in an unacceptable level of late toxicity in the form of radiation necrosis. Rosenthal and Glatstein cautioned that “stereotactic radiosurgery is really stereotactic radiotherapy, and when applied in single fraction to the treatment of cancer, it is suboptimal radiation oncology. Its utilization is virtually predicated on the ability to perform another craniotomy to remove focal necrosis” (5).

However, following many prospective and retrospective studies, this was found not to be the case (6, 7).

### Incidence

The exact incidence of radiation necrosis is largely unknown given the difficulties in accurately diagnosing it. Imaging techniques, as will be reviewed later, are largely imperfect. Biopsy, which is the gold standard, is subject to sampling error. Regardless, there are low rates of reoperation and autopsy. What is known is that incidence, in part, is a function of dose. In a study comparing low-dose versus high-dose radiation in the treatment of low-grade gliomas, the incidence of grade 3-5 radiation toxicity including radiation necrosis was 2.5% for 5040 cGy and 5% for 6480 cGy (8). Diagnostic criteria for radiation necrosis were not defined in this study.

In SRS, the incidence of radiation necrosis remains relatively low in contrast to the concerns raised by Rosenthal and Glatstein. According to Chin et al, the incidence of radiation necrosis following SRS is 7% (7). On the other hand, in a series of 310 lesions treated in Italy, there was a 24% risk of radiation necrosis, with 10% symptomatic and 14% asymptomatic radiation necrosis (9). This is likely because the Italian study used a unique set of criteria to define radiation necrosis: (1) increased T1 contrast enhancement in the radiated area with central hypointensity and increased edema, (2) substantial regression or stability for at least 4 months, and (3) a clear absence of perfusion in the absence of any nodular highly vascular area within the contrast-enhanced lesion on perfusion MRI. On the other hand, in Chin et al, radiation necrosis required pathological confirmation or resolution of a necrotic lesion over time. Clearly the incidence is impacted by how radiation necrosis is diagnosed and defined. For instance, at our institution, when we used a stricter criteria of radiation necrosis defined by decreased cerebral blood volume and/or decreased uptake by fluorodeoxyglucose (FDG) PET, our local control rate increased to 90% and 10% of our patients were found to have radiation necrosis (unpublished data).

### Table 1 Radiation injury based on time from radiation (2)

<table>
<thead>
<tr>
<th>Radiation injury</th>
<th>Time frame</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute injury</td>
<td>During or after completion of radiation</td>
<td>Reversible; characterized by edema</td>
</tr>
<tr>
<td>Early delayed injury (pseudoprogression)</td>
<td>Up to 12 weeks after radiation</td>
<td>Reversible; characterized by increased signal on fluid-attenuated inversion recovery abnormalities and T2</td>
</tr>
<tr>
<td>Late injury/radiation necrosis</td>
<td>Few months to years</td>
<td>Irreversible; focal pattern characterized by circumscribed lesion; diffuse pattern characterized by periventricular white matter changes</td>
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</table>

![Fig. 1. Magnetic resonance imaging (MRI) of radiation necrosis (T1 axial MRI with contrast) (a) before radiosurgery of arteriovenous malformation (AVM) and (b) after radiosurgery of AVM.](image-url)
was seen within the necrosis. Around the necrosis (perinecrotic area), the astrocytes are VEGF-positive. This likely stimulates the endothelial cell proliferation within the necrosis and perinecrotic tissue. HIF-1α is also seen in perinecrotic tissue, but little is found within necrotic tissue. This suggests that the management of radiation necrosis should focus more on the perinecrotic tissue, rather than the necrosis itself. Surgical resection of necrosis should also include the perinecrotic area.

**Presentation/Risk Factors**

Radiation necrosis is very difficult to distinguish from tumor recurrence. Both are morbid and symptomatic. In rare cases, radiation necrosis may result in death. Symptoms are no different than tumor recurrence and include headache, nausea, and somnolence (4). Routine imaging fails to distinguish between the two. On MRI, both have T2 changes representing edema. There is also blood-brain barrier disruption in both resulting in contrast-enhancement and a ring-enhancing lesion. Figure 1 shows an MRI image of radiation necrosis after Gamma Knife radiosurgery. Quick and accurate diagnosis, followed by timely treatment may reduce morbidity.

Risk factors, as demonstrated by studies to be discussed, include dose, fraction size, treatment duration, volume treated, chemotherapy, previous radiation, and male sex. Currently, there is no algorithm using these factors to assist in diagnosing radiation necrosis.

One of the oldest study on this subject looked at 152 patients treated in the mid-1970s for brain tumors, mostly gliomas, although some patients had pituitary tumors or did not have biopsy (16). Of these, 139 patients received 45 Gy or greater at 1.8-2 Gy per fraction, 5% of which developed radiation necrosis. This risk appeared to increase with larger fraction sizes when going from 60 Gy in 35 fractions to 60 Gy in 30 fractions. It also increased going above a dose of 54 Gy in 30 fractions.

For gliomas alone, total dose, fraction size, and chemotherapy appears to increase the risk for radiation necrosis (17). In this retrospective glioma study from Australia by Rubin et al, the incidence was 13% at 3 years. Beyond these factors, the authors also looked at diabetes, hypertension, age, gender, concurrent medications specifically steroids and anticonvulsants, pathology, and extent of resection. Of these, only age is a significant risk factor, but becomes insignificant when adjusted for biological equivalent dose or survival. Those at highest risk had a biological equivalent dose of ≥85.5 Gy², which is ≥45 Gy in 25 fractions. The authors concluded that radiation necrosis is uncommon with doses of 50 Gy in 25 fractions or less.

Specifically for intracranial radiosurgery, Radiation Oncology Therapy Group 90-05 was a dose escalation study of cranial SRS for recurrent brain metastases or gliomas and determined the maximum tolerated dose based on acute toxicity and chronic

### Pathophysiology

From rat brain experiments, it is known that white matter necrosis is a function of cumulative dose and duration of exposure (11). Rat brains were radiated at doses of 17.5, 20, 22.5, and 25 Gy in a single fraction. At intervals ranging from 13 to 52 weeks, the rats were sacrificed and their brains were examined histopathologically. Demyelination and necrosis was seen 39 weeks and greater with doses of 22.5 Gy or greater. This was time-dependent, with necrosis seen sooner at a dose of 25 Gy compared to 22.5 Gy. Gray matter necrosis was also seen.

Vascular injury initiates the process of necrosis. Vascular endothelial cell damage results in fibrinoid necrosis of the small arterial vessels. This leads to focal coagulative necrosis and oligodendrocyte damage and demyelination (12). Autoimmune vasculitis may also be seen (13).

More recently, vascular endothelial growth factor (VEGF) has been implicated (14, 15). Noland et al did single fraction radiation to rat spinal cords, starting at 8 Gy up to 22 Gy (14). Radiation-induced changes were seen from 18 to 22 Gy. Hypoxia-inducible factor 1α (HIF1α), VEGF, and glucose transporter-1 increased about 20 weeks after delivering 18 Gy to the spinal cord, before the development of paralysis. HIF1α and VEGFexpressing cells were identified as astrocytes, VEGF was identified as a target to prevent and treat radiation injury/necrosis, which will be discussed later.

Nonoguchi et al assessed 11 pathological samples of radiation necrosis with anti-VEGF antibody and anti-HIF1α (15). No VEGF

### Table 2 Risk of radiation necrosis based on dose and volume

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Volume</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korytko et al (2006) (19)</td>
<td>12 Gy</td>
<td>&gt;10 mL</td>
<td>&gt;50% (compared with 20%)</td>
</tr>
<tr>
<td>Minniti et al (2011) (9)</td>
<td>12 Gy</td>
<td>&gt;10.9 mL</td>
<td>47%</td>
</tr>
<tr>
<td>Blonigen et al (2010) (20)</td>
<td>10 Gy</td>
<td>&gt;10.5 mL</td>
<td>35%</td>
</tr>
</tbody>
</table>

### Table 3 Comparative data on lesion quotient

<table>
<thead>
<tr>
<th>Author</th>
<th>Test</th>
<th>Sensitivity (%) for predicting radiation necrosis alone</th>
<th>Specificity (%) for predicting radiation necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dequesada et al</td>
<td>Standard MRI—lesion quotient</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>Kano et al</td>
<td>Standard MRI—T1/T2 mismatch</td>
<td>83.3</td>
<td>91.1</td>
</tr>
<tr>
<td>Stockham et al</td>
<td>Standard MRI—lesion quotient</td>
<td>8</td>
<td>91</td>
</tr>
</tbody>
</table>

Abbreviation: MRI = magnetic resonance imaging.

Despite using imaging techniques to rule out the possibility of radiation necrosis, in a series of patients who underwent resection post SRS, 10% were found to have radiation necrosis alone (10). Patients were followed after Gamma Knife radiosurgery per routine. When there was an increase in size of the lesion, MRS or perfusion scans were obtained to rule out radiation necrosis. Those with progression underwent resection, but only 90% had true progression. In 9 of 11 tumors, MRS predicted for tumor correctly, but 2 of 3 lesions diagnosed by MRS to be radiation necrosis actually contained tumor. This illustrates the limitations of current imaging techniques and also highlights that radiation necrosis is underreported.

### Presentation/Risk Factors

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contribute to radiation necrosis (19). In Minnitti et al. and Blonigen brain radiation, and male sex. Interestingly, conformality did not necrosis include occipital and temporal lesions, previous whole to 50%. In Korytko et al, other factors that contribute to radiation 10-12 Gy. At this volume, the risk for radiation necrosis may be up consistent factor amongst these studies is 10 mL or more receiving tumors beyond A VMs. This is summarized in Table 2. The augmented by the 12-Gy volume. Given the variability of risk for SRS were 24 Gy for tumors <20 mm, 18 Gy for tumors 21-30 mm, and 15 Gy for tumors 31-40 mm. For intracranial radiosurgery, an arteriovenous malformation (AVM) is a good disease model to study radiation necrosis. It is easier to diagnose radiation necrosis simply based on progression of enhancement, unlike tumors in which progression of the enhancing lesion may be tumor progression. Also, a variety of doses are used, and different volumes and locations treated allow for these factors to be analyzed. Flickinger et al used this model to study radiation necrosis and found that the 12 Gy volume and location was predictive of radiation necrosis (18). A Significant Postradiosurgery Injury Prediction location risk score was developed. In summary, risk varied with location with the frontal lobe being the lowest risk and pons/ midbrain location being the highest risk. This risk is further augmented by the 12-Gy volume. Given the variability of risk depending on location, this model requires graphs provided in their articles, making it hard to use by the bedside, but is probably the most accurate model in predicting radiation necrosis in patients with AVM.

The 12-Gy volume was also found to be significant in other tumors beyond AVMs. This is summarized in Table 2. The consistent factor amongst these studies is 10 mL or more receiving 10-12 Gy. At this volume, the risk for radiation necrosis may be up to 50%. In Korytko et al, other factors that contribute to radiation necrosis include occipital and temporal lesions, previous whole brain radiation, and male sex. Interestingly, conformality did not contribute to radiation necrosis (19). In Minnitti et al and Blonigen et al, location did not appear to increase risk of radiation necrosis (9, 20).

### Diagnosis

Diagnosing radiation necrosis is complicated by the fact that very few studies correlate imaging techniques with pathological information because of low rates of resection or biopsy. CT and MRI typically reveal a ring-enhancing lesion with surrounding edema, which is also consistent with tumor recurrence. A couple of studies looked at the concept of lesion quotient (LQ), which is the ratio of the nodule seen on T2 compared with the total enhancing area seen on T1. In the Desquesada et al study, 32 patients were analyzed having adequate MRI follow-up and surgical pathology out of a total of 619 patients treated with LINAC radiosurgery (21). A LQ of 0.6 or greater was seen in all cases of recurrent tumor, whereas LQ of 0.3 or less was demonstrated in 4 of 5 cases of radiation necrosis. LQ of greater than 0.3 was seen in 19 of 20 combination pathology. The negative predictive value of the lesion quotient (>0.3) for radiation necrosis was 96%, resulting in 80% sensitivity and 96% specificity. This would make LQ a reliable tool for determining radiation necrosis without the need of additional imaging.

A less quantitative method of LQ relies on correlating the tumor margins on T1 with the tumor margin on T2, known as T1/T2 mismatch (22). If these margins correlate well, the lesion is consistent with tumor recurrence. If they do not correlate, this would be radiation necrosis. This is a facile way of diagnosing radiation necrosis and was investigated using a population of 68 patients treated with Gamma Knife who later underwent resection. In this study, the sensitivity of T1/T2 mismatch was 83.3% and the specificity was 91.1%.

The Desquesada et al study was repeated at our institution with a similar patient population, except patients were treated with Gamma Knife radiosurgery instead of LINAC radiosurgery (23). Unfortunately, this study did not reproduce the results of the Desquesada group. Using the same definition for LQ, the authors found that the sensitivity was 8% and the specificity was 91%. Several other factors were analyzed including gender, radiosurgery dose, prior whole brain radiation, maximum dose, conformality index, and heterogeneity index. None of these factors was significant, although maximum dose approached significance. Table 3 compares the results of Desquesada et al with Stockham et al. At our institution, LQ is not used.

Cerebral blood volume has been postulated to be increased in tumor and decreased in radiation necrosis. This was evaluated in 27 patients with brain metastases treated with radiosurgery (24). The patients with recurrence had a relative cerebral blood volume (rCBV) ranging from 2.1 to 10. In radiation necrosis, rCBV ranged from 0.39 to 2.57. The optimum rCBV threshold was determined to be 2.1 and using this threshold results in a sensitivity of 100% and specificity of 95.2%. Based on these limited data, rCBV is potentially a tool in distinguishing radiation necrosis from tumor recurrence.

FDG PET has been used and investigated on the principle that tumor metabolism increases FDG uptake and radiation necrosis would have decreased uptake. The main issue with the use of FDG PET is that methodologies vary. Because uptake from the mass must be compared with normal tissue, it is undefined whether this should be adjacent cortex activity, adjacent gray-white matter junction, adjacent white matter, or adjacent gray matter. Likely as a consequence, differing sensitivities and specificities have been reported. Again, very few of these studies use pathological confirmation.

The use of FDG PET was investigated at our institution and reported in 2001 (25). This study involved 47 patients who had presumed radiation necrosis versus tumor recurrence after stereotactic radiosurgery. Adjacent gray/white matter junction was used as comparison. Of note, 14 of these patients had MRI co-registration, which was not commonly used at that time. Overall, FDG PET was 75% sensitive and 80% specific. Specifically with brain metastases, for those without MRI coregistration, FDG PET was 65% sensitive and 80% specific.
MRI coregistration increased the sensitivity to 86% with the same specificity. Kim et al showed similar results (26). Although not completely accurate, it is helpful in establishing a diagnosis.

Other studies looking at PET show mixed results. Ricci et al found this technique to not be specific (27), whereas Thompson et al demonstrates this not to be sensitive (28). Table 4 summarizes these results. Regardless, PET is overall felt to be an imperfect technique.

Other PET radiotracers have been used because of the limitations of FDG-PET, specifically concerns of uptake by normal cortex, lack of uptake by low-grade gliomas, uptake by abscess, and uptake by the inflammation from radiation necrosis. Other agents being investigated include carbon-11-methyl-methionine; O-(2-[18F]fluorothyl)-L-tyrosine; 3,4-dihydroxy-6-[18F]fluoro-phenylalanine (FDOPA); and 3-O-methyl-6-[18F]fluoro-L-DOPA. For instance, FDOPA, which is an amino acid analog of phenylalanine, was assessed in a small study by Chen et al in 2006 (29). Eighty-one patients were studied. Depending on the threshold used, 96% sensitivity and 100% specificity may be achieved. They used the threshold of the ratio of tumor to normal striatum >1.0. There was a statistically significant difference in uptake levels between tumor and radiation necrosis (P >.00001). When compared using visual inspection to patients also imaged with FDG PET, the sensitivity for FDOPA PET is 96% versus 61% for FDG PET.

Other nuclear medicine modalities have been investigated, namely thallium-201 (Tl) SPECT. In a study of 72 patients, Tl SPECT was used to distinguish radiation necrosis from tumor recurrence (30). Radiation necrosis was defined with an index <3.0. Index >5.0 was defined as tumor recurrence. Those in between those 2 values were scanned once a month for 2 months until it fell within one of those values. Those that remained within the 2 values afterward were defined as radiation injury. Using this approach and thresholds, sensitivity was 90% and specificity was 90.5%. However, just like PET with conflicting studies, other studies have shown Tl SPECT to be no different than FDG PET (31).
MRS provides information on the metabolic composition within the tissue and remains a promising technique to distinguish tumor from recurrence. With MRS, imaging time is extended by 15 to 30 minutes to acquire the data. The metabolites analyzed include lipids (which represents the product of brain destruction), lactate (representing anaerobic glycolysis), NAA (neuronal marker), glutamine (neurotransmitter), creatine (energy metabolism), and choline (cell membrane marker). In a small study of 9 patients using FDG PET, single-voxel MRS, and multivoxel MRS, Chernov et al defined Lipid (Lip)/Choline (Cho) >3 as necrosis, and tumor recurrence was defined as NAA/Cho <1 and Lip/Cho <3 in any voxel (32). In terms of predicting for radiation necrosis, FDG PET had a sensitivity of 50% and a specificity of 80%, respectively. On the other hand, single-voxel MRS had a sensitivity of 50%, but a specificity of 100%. With multivoxel MRS, sensitivity and specificity were 100%. Despite these results, given the small sample size, MRS remains investigational (33).

Despite numerous studies assessing novel imaging techniques for radiation necrosis, the studies are all small and there is no established radiographic method to diagnose radiation necrosis. Larger studies are needed.

Treatment

Some cases of radiation necrosis may be observed. In a study of 124 patients who had radiation for nasopharyngeal carcinoma and developed imaging changes in the temporal lobe, 28% of white matter lesions, 39% of contrast-enhanced lesions, and 7% of cysts regressed or resolved (34). Radiation necrosis is not always a progressive process. Observation can be considered for patients who are asymptomatic or if the lesion is small.

Because radiation necrosis is associated with significant swelling, steroids may be used. Resection is reserved for steroid refractory radiation necrosis or in situations in which the diagnosis is unclear. Other management options include anticoagulants such as heparin and warfarin, which presumably arrests and reverses small vessel vascular injury, controlling the necrosis (35). In a study by Glantz et al, 8 of 11 patients had clinical improvement with anticoagulants. Anticoagulation was continued for 3 to 6 months. Only one had recurrence of symptoms after discontinuation of anticoagulation, which improved after reinitiating therapy. More recently, a small case series looked at patients who underwent anticoagulation for radiation injury (36). Two of the 3 patients with cerebral lesions and 1 patient with a lesion on a cranial nerve had modest symptomatic improvement with no treatment toxicity. The authors of this series suggest coupling anticoagulation with other therapies in a prospective study given modest benefit with anticoagulation alone.

Given the reported improvement of radiation damage in other organ systems, Williamson et al looked at using oral vitamin E and pentoxifylline in a pilot study of 11 patients (37). There was improvement, with exception of 1 patient who had worsening of edema, but this was later found to be tumor recurrence, not radiation effect. Two patients discontinued pentoxifylline because of persistent nausea and abdominal discomfort.

Another treatment option is hyperbaric oxygen (HBO) in which patients are placed into a chamber with 100% oxygen that
is increased to 2.5 times atmospheric pressure. This forces oxygen into the blood plasma and into the tissues and encourages new vessels to grow. This is given up to 5 days a week and may need 30 to 40 treatments to see benefit. Despite the long-time use of HBO, data for this therapy are sparse and limited to case studies (38, 39). There is stronger evidence, however, that HBO may be used as a prophylaxis to prevent radiation necrosis. In a study by Oghuri et al, 32 patients received HBO less than 1 week after SRS (40). HBO was delivered using 15 minutes with compression of air, 60 minutes of 100% oxygen inhalation at 2.5 times atmosphere, and 10 minutes of decompression for a total of 20 sessions, 5 days per week. Radiation-induced brain injury occurred in 11% of these patients, compared with 20% in patients not receiving HBO prophylaxis when studied retrospectively. HBO may be used to minimize the risk of radiation necrosis in patients at high risk for radiation necrosis.

The therapy with the best supported evidence is bevacizumab. Because VEGF is dysregulated with radiation necrosis and bevacizumab presumably controls VEGF, it can reverse the effects of radiation necrosis. Bevacizumab was given to 8 patients with radiation necrosis and all patients showed a reduction in fluid-attenuated inversion recovery abnormalities (FLAIR) and T1-weighted post-gadolinium abnormalities (41). There was also a reduction in dexamethasone dose. This result was confirmed at another institution with a series of 6 patients with biopsy-confirmed radiation necrosis (42). A double-blind, placebo-controlled trial was conducted at MD Anderson (43). In this study, patients were randomized to receive placebo or intravenous bevacizumab at a dose of 7.5 mg/kg at 3-week intervals for 2 treatments. Those responding would continue on for another 2 cycles. Those not responding to the initial therapy crossed over to the other treatment arm. A total of 14 patients were randomized. None of the 7 receiving placebo responded with either improvement of MRI findings or neurological signs and symptoms. All of the patients receiving bevacizumab improved with decreases in T(2)-weighted FLAIR and T(1)-weighted gadolinium-enhanced volumes. Those receiving bevacizumab also had improvement in neurological signs and symptoms. At our institution, these results were confirmed with a larger series of patients (unpublished data). Radiographic improvement was seen in 23 of 24 patients, with only one patient with a grade 3 adverse event.

Although bevacizumab is the best supported therapy for radiation necrosis, using this drug has limitations. These include patients with cerebral hemorrhage or non-small cell lung cancer with squamous cell histology. Also there is concern with “overpruning,” in which there may be resulting vascular insufficiency and worsening radiation necrosis (44). This occurred in a patient who was treated for a low-grade glioma and 1 year after radiation developed biopsy proven radiation necrosis. He was started on bevacizumab with improvement after 1 month, but over the next 3 months, he symptomatically declined with radiographic progression. Biopsy reconfirmed radiation necrosis. The authors concluded that possibly bevacizumab could make radiation necrosis worse by causing vascular insufficiency and worsening hypoxia.

Because bevacizumab also has antineoplastic effects, similar to resection, this drug can be used to treat any tumor with progressive enhancement and FLAIR changes postradiation, although the diagnosis as to the cause of progression may be unclear or difficult to establish. Also as an alternative to resection, focused interstitial laser therapy may be used to treat progression of enhancement either from tumor progression or radiation necrosis. This therapy has been shown to effectively treat radiation necrosis (45). Figure 2 shows the treatment of radiation necrosis with focused interstitial laser therapy. In the setting of radiation necrosis, this laser may ablate the VEGF producing reactive astrocytes as discussed previously, although the true mechanism remains unclear. This therapy is being studied in a multi-institutional prospective phase 2 study, Laser Ablation After Stereotactic Radiosurgery. For patients with any progression after stereotactic radiosurgery, some of these patients will likely have radiation necrosis. In this study, a biopsy is obtained before laser ablation to determine its exact role in radiation necrosis versus tumor recurrence.

**Additional Challenges**

Currently, given the challenges in diagnosing and treating radiation necrosis, a legitimate question is whether doing so changes patient outcomes. In a study at University of California, San Francisco, in patients with glioblastoma multiforme (GBM) who underwent a second surgery after radiation, the diagnosis of radiation necrosis versus tumor recurrence did not impact overall survival (46). It is important to note that these patients were treated in an era when options for recurrent disease and radiation necrosis were limited, specifically 1989 to 2002. Conversely more recently, Rustohoven et al demonstrated increased survival in GBM patients with radiation necrosis after second surgery compared with patients with tumor recurrence (21.8 months vs 7.0 months, \( P = .047 \)) (47). Beyond survival, quality of life and reduction of morbidity are important endpoints that may be impacted with early diagnosis and treatment and should be assessed in future studies. Moving forward, however, it will be important to demonstrate benefit in diagnosing radiation necrosis early and treating these patients aggressively as treatment modalities for tumor recurrence and radiation necrosis continue to evolve. Many of the diagnostic and treatment modalities mentioned here are costly, which is an important consideration given the high cost of healthcare. The Laser Ablation After Stereotactic Radiosurgery trial mentioned previously may help address these questions.

There is also a question on how best to treat lesions with both tumor recurrence and radiation necrosis. Are these lesions better treated as tumor recurrence or radiation necrosis? This brings up the question how best to determine sensitivity and specificity of our diagnostic tools because there may be 3 possibilities (tumor recurrence, radiation necrosis, and mixed tumors/combination pathology), not just 2. This was addressed in some of the mentioned studies, but not all. This will need to be considered in the design of future studies. For mixed tumors, because tumor recurrence may result in worse outcomes, our institutional bias is to treat these lesions as tumor recurrence. In addition, current therapies such as bevacizumab and laser interstitial therapy treat both simultaneously, reducing the need for accurate diagnosis and allow for some uncertainty.

Finally, developing a better approach to diagnosing and treating radiation necrosis may overcome fears regarding this complication. Historically, dose-intensification studies were limited given issues concerning radiation necrosis. With more accurate diagnosis of tumor recurrence, the endpoint of local control also becomes more accurate by not being misdiagnosed with radiation necrosis. With better treatment of radiation necrosis, perhaps a higher rate of radiation necrosis is acceptable...
if better tumor control is achieved by dose intensification or combined modality therapy, resulting in improved survival (47). In the case with GBM, this may mean higher doses (48) or a hypofractionated regimen (49). Similarly, it has been shown that lower doses of SRS are insufficient to control large brain metastases (50), and perhaps, going to higher doses and managing the radiation necrosis may provide better outcomes. Higher doses of SRS for larger brain metastases are being assessed at our institution, recognizing that this may result in a higher rate of radiation necrosis.

**Conclusion**

Despite the rising incidence of radiation necrosis because of increased utilization of stereotactic radiosurgery and repeat brain irradiation, there remains significant challenges in the diagnosis of radiation necrosis. To date, there is no established standard to noninvasively diagnose radiation necrosis. Over the past few years, there are, however, more treatment options for radiation necrosis, particularly with bevacizumab. More studies are needed to better 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. In the meantime, Figure 3 illustrates a possible algorithm to diagnose and treat radiation necrosis. Perhaps with more awareness, more studies will follow.

**References**


