Commentary on:
Laser-Interstitial Thermal Therapy for Refractory Cerebral Edema from Post-Radiosurgery Metastasis
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The Pathophysiology of Cerebral Radiation Necrosis and the Role of Laser Interstitial Thermal Therapy

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Stereotactic radiosurgery can effectively ablate brain tumors; however, it also has the potential to cause tissue injury around the tumor site. The acute effects on the brain tissue are usually reversible; they occur <2 months after radiotherapy and result from endothelial cell apoptosis, which causes disruption of the blood-brain barrier and peritumoral edema (20, 22, 33). Acute radiation injury also incites inflammatory pathways, which are accelerated by chronic hypoxia secondary to endothelial remodeling, further setting the stage for "microenvironmental change" (33). If this process continues to evolve, the result is irreversible cerebral radiation necrosis (RN).

Although breakdown of the blood-brain barrier may enhance the effectiveness of chemotherapeutic agents, these agents also contribute to peritumoral tissue damage (33). Cerebral RN most often manifests as a late, delayed radiotherapy effect, which may occur 3–12 months after chemoradiotherapy, although cases can occur 2 years after treatment (14, 33). Patients with cerebral RN present with seizures, signs and symptoms of increased intracranial pressure, cognitive dysfunction, or focal neurologic deficits depending on the location of the lesion (14, 28). Cerebral RN after focal irradiation has an incidence of 1%-24% (6, 19, 21, 30, 32-34). However, this rate may be three times higher with concurrent chemotherapy (5, 8, 11).

The magnetic resonance imaging appearance of cerebral RN consists of contrast enhancement, which Kumar et al. (19, 33) described as remote or new "Swiss-cheese or soap-bubble enhancement." However, tumor recurrence manifests as described by Mullins et al. (23, 33) invasion of the corpus callosum with 1) crossing of the midline and multiple lesions or with 2) subependymal spread with or without multiple lesions. Other modes of imaging must be used to differentiate these two entities. Perfusion magnetic resonance imaging assesses the vascularity and hemodynamics of tumors by measuring the relative cerebral blood volume (2, 33). Hyperperfusion is seen with tumor recurrence (2, 10, 33) because tumors have increased metabolic activity and neoangiogenesis, the latter resulting from the increased expression of vascular endothelial growth factor (VEGF) (17, 33). Conversely, cerebral RN shows low regional relative cerebral blood volume, owing to occlusive vasculopathy, which causes ischemia-related changes (7, 13, 17). Another differentiating imaging tool is diffusion-weighted imaging, which detects the magnitude and rate of free water movement in tissues (1, 35). These entities are quantified with diffusion-weighted imaging via the (*a*) apparent diffusion coefficient for magnitude and (*b*) diffusion tensor imaging for direction (1). A high apparent diffusion coefficient is seen with cerebral RN as a result of increased water mobility in the RN tissue (7). Tumor progression demonstrates high choline, reduced *N*-acetyl aspartate, and increased lactate the latter in necrotic tumors on magnetic resonance spectroscopy, whereas cerebral RN shows low choline with high lactate (7, 24). On thallium-201 single photon emission computed tomography and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, low tracer uptake is seen with cerebral RN (7).

Microscopically, cerebral RN demonstrates white matter necrosis, fibrinoid necrosis, vessel thrombosis, telangiectasia, calcification, and macrophage infiltration throughout (3, 14, 24). Compared with tumor cells, cerebral RN contains cells with fewer mitotic figures and a lower nucleus-to-cytoplasmic ratio (24, 27).

Key words
- Edema
- Laser
- Metastasis
- Necrosis
- Radiation
- Thermal

Abbreviations and Acronyms
LITT: Laser interstitial thermal therapy
RN: Radiation necrosis
VEGF: Vascular endothelial growth factor

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Treatment of cerebral RN includes corticosteroids, surgical lesion removal, and anticoagulation with warfarin alone (28, 29) and heparin and warfarin (15, 28). Williamson et al. (28, 37) used pentoxifylline, a methylxanthine derivative that increases blood cell deformity and decreases viscosity enhancing circulation. The investigators combined pentoxifylline with the free radical scavenger vitamin E, which reduces early and late radiation-induced adverse effects (28). By increasing tissue oxygen, hyperbaric oxygen has been used to counteract the cascade of hypoxia-induced hypoxia inducible factor 1 alpha releasing intracellular adhesion molecule-1 and cytokines which in turn facilitate breakdown of the blood-brain barrier which results in cerebral RN (25, 28).

Bevacizumab (Avastin) is an anti-VEGF antibody that has been used to treat cerebral RN. Boothe et al. (4) evaluated 14 cerebral RN lesions in 11 patients; 5 of the patients had breast cancer, and 6 had non–small cell lung carcinoma. All patients had undergone stereotactic radiosurgery, and bevacizumab was used to treat RN lesions. At a mean of 26 days after treatment was begun, the lesions had shrunk to 64.4% and 64.3% on T1-weighted post-gadolinium and fluid-attenuated inversion recovery magnetic resonance imaging sequences, respectively. The changes were sustained after discontinuation of treatment on follow-up scans at a mean of 33 days. All patients but one had an improvement in cerebral RN–associated symptoms. However, bevacizumab is costly, has the potential for severe side effects, and requires long-term use to be effective in reversing cerebral RN (28). Minimally invasive procedures used to treat cerebral RN include cryoablation, high-frequency ultrasound, radiofrequency ablation, and laser interstitial thermal therapy (LITT) (28).

Using the described differentiating techniques does not always accurately determine the presence of cerebral RN versus tumor recurrence because pure cerebral RN without recurrent tumor is uncommon. Cerebral RN usually is mixed with recurrent tumor tissue, so there are combinations of imaging findings, which do not allow a precise and isolated diagnosis of cerebral RN. To confuse the picture further, Na et al. (24) performed an extensive literature review and found that few articles distinguished pure cerebral RN from cerebral RN mixed with tumor recurrence. They also found that some publications included patients exhibiting cerebral RN who, in addition to receiving radiotherapy, were also undergoing concomitant adjuvant chemotherapy, the latter of which may have affected the histologic features of cerebral RN. To make matters even more perplexing, the present article by Fabiano and Alberico did not include the results of the above-mentioned imaging studies, and histology was not obtained before or during LITT treatment. The authors stated, "It is possible that the lesion treated in this case was recurrent metastatic tumor, rather than RN." To expand this statement further, it possible that LITT was treating cerebral RN, recurrent tumor, or varying amounts of cerebral RN and recurrent tumor.

Rahmathulla et al. (28), who presented another case of cerebral RN that was successfully treated with LITT, obtained histologic verification of cerebral RN, which was confirmed with positron emission tomography/computed tomography scanning showing the lesion to be hypometabolic and with diffusion-weighted imaging, which revealed restricted diffusion, both of which supported the diagnosis of cerebral RN. Although the lesion was likely pure cerebral RN per imaging, the authors did not describe whether it may have been pure cerebral RN or whether it was a mixture of predominantly cerebral RN and a few recurrent tumor cells.

Table 1. Pathophysiology of Radiation Necrosis

Vascular
Endothelial cell injury and apoptosis (26)
Increased vascular permeability and edema (16)
Expression of von Willebrand factor, prostacyclin, and plasminogen activator with inflammatory cell vessel infiltration (9)
Chronic endothelial damage, thrombosis, vessel wall thickening, and fibrosis (9, 16)
Tissue hypoxia and necrosis
VEGF expression, angiogenesis (38)
Telangiectasia, edema
Chronic reperfusion-reperfusion injury due to prothrombotic vessels (16)
Glial
Axonal swelling, reactive gliosis (9)
Oligodendrocyte injury, demyelination and white matter necrosis (18)
Neuronal
Edema disrupts proximity of progenitor cells to microvasculature
Apoptosis of neural progenitors and impairment in hippocampal neurogenesis (12)
Enzymatic
Abnormal fibrinolytic enzyme function (31)
Reduced tissue plasminogen activator disrupts fibrinogen function (31)
Excess urokinase activates extracellular proteolysis (31)
Inflammatory
Overexpression of inflammatory [cells] and cytokines (tumor necrosis factor-α, interleukin-1 and 6) (38)
Increased vascular permeability to inflammatory cells (12)
Chronic inflammation with release of reactive oxygen intermediates (36)

VEGF, vascular endothelial growth factor.
From Na A, Haghigi N, Drummond KJ: Cerebral radiation necrosis. Asia Pac J Clin Oncol 10:11-21, 2014 [24]. Reprinted with permission from John Wiley and Sons.

Rahmathulla et al. (28) presented the hypothesis that the rationale for the use of LITT to treat cerebral RN was that LITT would "replace the endothelial proliferating cells and zone of disorganized angiogenesis with thrombosed vessels." The perinecrotic (i.e., gliotic) zone was also included in their treatment volume. Their target region consisted of the necrotic center, the contrast-enhancing periphery, and the perinecrotic gliotic zone with the addition of a margin of approximately 0.5 cm surrounding the target lesion. These authors stated that "functionally, the perinecrotic zone is responsible for much of the VEGF release," the latter of which is a potent angiogenic peptide resulting in vasogenic edema, which also helps to increase hypoxia inducible