Malignant Gliomas: MR Imaging Spectrum of Radiation Therapy– and Chemotherapy-induced Necrosis of the Brain after Treatment

PURPOSE: To describe both the common and less frequently encountered magnetic resonance (MR) imaging features of radiation therapy– and chemotherapy-induced brain injury, with particular emphasis on radiation necrosis.

MATERIALS AND METHODS: A cohort of 148 adult patients underwent surgical resection of malignant brain (glial) tumors and were subsequently entered into a research protocol that consisted of accelerated radiation therapy with carboplatin followed by chemotherapy with procarbazine, lomustine, and vincristine. Patients typically underwent sequential MR imaging at 6–8-week intervals during the 1st year and at 3–6-month intervals during subsequent years. In all patients, histopathologic confirmation of lesion composition was performed by board-certified neuropathologists.

RESULTS: The patients exhibited different types of MR imaging–detected abnormalities of the brain: pure radiation necrosis in 20 patients, a mixture of predominantly radiation necrosis with limited recurrent and/or residual tumor (less than 20% of resected tissue) in 16 patients, radiation necrosis of the cranial nerves and/or their pathways in two patients, radiation-induced enhancement of the white matter in 52 patients, and radiation-induced enhancement of the cortex in nine patients.

CONCLUSION: The frequent diagnostic dilemma of recurrent neoplasm versus radiation necrosis is addressed in this study through a description of the varying spatial and temporal patterns of radiation necrosis at MR imaging.

During the past decade, the treatment of malignant gliomas has benefitted from several advances, including early detection of tumors by using magnetic resonance (MR) imaging, improvements in neurosurgical instrumentation that have facilitated more precise radical resection of neoplasms, advances in the delivery of radiation doses to tumors, and new chemotherapeutic protocols. However, the sequential MR images obtained in these patients have demonstrated a variety of radiation therapy– and chemotherapy-induced changes in the brain. Radiation necrosis is the most substantial and most severe form of radiation-induced injury with therapeutic implications. The diagnosis of radiation necrosis at imaging has been challenging, primarily because the pattern of abnormal enhancement closely mimics that of recurrent brain tumor. The purpose of this retrospective study was to review our experience with the MR imaging spectrum of radiation necrosis.

MATERIALS AND METHODS

One hundred forty-eight patients (82 men, 66 women; mean age, 41 years; age range, 18–75 years) with malignant gliomas—92 with glioblastoma multiforme, 40 with anaplas-
tic astrocytoma, nine with anaplastic mixed glioma, and seven with anaplastic oligodendroglioma—were entered into research protocol DM88-113 after they gave institutional review board–approved informed consent and after undergoing either total or subtotal resection of their tumors (1). After surgery, the patients received accelerated fractionation radiation therapy and concomitant carboplatin-based chemotherapy. The accelerated radiation therapy consisted of three doses of 1.9–2.0 Gy each per day, with a 4-hour interval between fractions. Carboplatin was given intravenously for 2 hours at a dose of 33 mg/m², 1.75 hours before each radiation treatment. This regimen was administered with a 6-MV linear accelerator for 5 consecutive days. After a 2-week break, a second course of treatment identical to the first was given so that a total dose of 57–60 Gy was given; the majority of patients received 57 Gy following an amendment to the protocol.

The radiation portal was generally limited to a 2–3-cm margin around the enhancing tumor and the nonenhancing abnormal tumoral signal intensity (not edema), if present, at T2-weighted imaging. In tumors that were closer to the midline—for example, corpus callosal tumors—partially opposing portals were used and resulted in margins wider than 3 cm in the lateral dimension. Postradiation chemotherapy consisted of procarbazine, lomustine, and vincristine, beginning within 4 weeks after the completion of radiation therapy. The administration of procarbazine, lomustine, and vincristine was repeated at 6-week intervals for 1 year or until tumor progression.

The preoperative and postoperative follow-up MR images of the brain obtained in the 148 patients were reviewed by two authors (A.J.K., N.E.L.), and the findings were tabulated by means of consensus. The information gathered from the MR images consisted of (a) the enhancing or nonenhancing features of primary neoplasm, (b) the appearance and location of recurrent enhancing lesions, single or multiple, (c) the proximity of the recurrent lesion to the primary tumor, and (d) the interval between the end of radiation therapy and the histopathologic confirmation of radiation necrosis. The MR images of the brain consisted of standard nonenhanced and contrast material–enhanced studies that were obtained both at our institution and at outside imaging centers.

At our institution, the MR images of the brain, which were obtained by using a 1.5-T unit (Signa Horizon SX; GE Medical Systems, Milwaukee, Wis), consisted of transverse T2-weighted (2,000–3,000/80–100 [repetition time msec/echo time msec], one signal acquired) and intermediate-weighted (2,000–3,000/20–30, one signal acquired) images and pre- and postcontrast transverse, T1-weighted, spin-echo images (500–600/8–16, two signals acquired). The postcontrast transverse and coronal T1-weighted images were obtained by administering gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) intravenously at a dose of 0.1 mmol per kilogram of body weight. Occasionally, sagittal postcontrast T1-weighted images of the brain also were obtained as needed.

In the patients in the DM88-113 protocol, postsurgical follow-up MR images were obtained either within 72 hours or 2–4 weeks after surgery. Follow-up MR images were obtained within 2 weeks after completing radiation therapy and at 6–8-week intervals during the procarbazine, lomustine, and vincristine treatment period. During year 2 after treatment, follow-up MR images were obtained at 3-month intervals; during year 3, at 4-month intervals; and during year 4, at 6-month intervals. If clinical deterioration occurred, MR images were obtained as needed.

Histopathologic examination of 36 surgically resected tissue specimens—nine by means of stereotactic biopsy and 27 by means of open resection—was performed by board-certified neuropathologists (one of which was G.N.F.). The autopsy results in nine patients also were available.

RESULTS

Therapy-induced necrosis in the brain, which was proved at histopathologic examination, was found in 22 of the 56 patients with anaplastic gliomas and in 14 of the 92 patients with glioblastomas under protocol DM88-113. The necrosis of the brain was attributed to the combined effects of radiation therapy and chemotherapy. Isodose curves revealed that all of the radiation-induced necroses occurred within the radiation portal. Analysis of the long-T2-weighted images was not found to be helpful in differentiating recurrent tumor from radiation necrosis.

Twenty of the 36 surgical specimens had histopathologic evidence of radiation necrosis with no evidence of tumor, and 16 had evidence of a mixture of extensive necrosis with residual and/or recurrent tumor (less than 20% of resected tissue). The common and uncommon features of radiation necrosis included radiation necrosis simulating a recurrent glioma at the site of the surgical cavity (Fig 1), distant to the site of the primary tumor on the ipsilateral side (Fig 2), or on the contralateral side (Fig 3), and multiple radiation-induced necrotic masses simulating multiple metastases (Fig 4a) and/or multiple sclerosis (Fig 4b).

The MR imaging features commonly seen in radiation necrosis are a soap bubble–like interior (Fig 4a) and a Swiss cheese–like interior (Fig 5). The MR imaging characteristics of radiation necrosis in both groups—that is, in the patients with pure radiation necrosis and in those with predominantly radiation necrosis—are outlined in the Table. In the 20 patients with pure radiation necrosis, the primary tumor was nonenhancing in 10 anaplastic gliomas and enhancing in 10 tumors—three anaplastic gliomas and seven glioblastomas. In the 16 patients with necrosis intermingled with tumor, the primary tumor was enhancing in three anaplastic gliomas and seven glioblastomas and nonenhancing in six anaplastic gliomas. Infratentorial radiation-induced necrosis following radiation therapy for parietal lobe glioblastoma is illustrated in Figure 6. The intervals from completion of radiation therapy to histopathologic confirmation of necrotic lesions in both groups are illustrated in Figure 7.

Radiation-induced enhancement in the brain without radiation necrosis was observed in the white matter (Fig 8) in 52 patients and in the cortex (Fig 9) in nine patients. Radiation-induced necrosis of the optic pathway (Fig 10) was seen in one patient, and radiation-induced necrosis of the auditory pathway (Fig 11) was seen in one other patient.

DISCUSSION

Pathophysiology of Radiation-induced Damage to the Brain

Currently, a complete understanding of the pathophysiology of radiation therapy– and chemotherapy-induced injury to the central nervous system is lacking. Relevant variables include total radiation dose, radiation field size, radiation fraction size, number and frequency of radiation doses, combination of radiation therapy and chemotherapy, duration of survival, and age of the patient at treatment (2). Understanding the importance
of specific MR imaging findings in this patient population is aided by a familiarity with the current concepts of the pathophysiology of radiation-induced damage to the central nervous system, which are reviewed in the following text.

The postulated mechanisms that may contribute to radiation-induced neurotoxicity include (a) vascular injury, (b) glial and white matter damage, (c) effects on the fibrinolytic enzyme system, and (d) immune mechanisms.

Vascular injury.—In acute radiation-induced injury, transient vasodilatation occurs with variable changes in capillary permeability that sometimes manifest as vasogenic edema (3,4). Changes in capillary permeability, in response to radiation therapy to the central nervous system, have been quantitated and found to entail specific molecular-size variability (5,6). In chronic radiation-induced injury, vascular endothelial damage takes place (4). Fike et al (7) demonstrated in animal studies that vascular abnormalities occur before the development of parenchymal changes in the brain. The pathologic findings consist of endothelial damage, vascular ectasia, and telangiectasia, all of which result in increased...
capillary permeability at the site of vascular injury with resultant cytotoxic and vasogenic edema (4). Progressive vascular changes include vessel wall thickening caused by hyalinization, with consequent thrombosis, infarction, and necrosis (4). The results of these studies provide support for the concept that vascular injury has a pivotal role in the development of radiation-induced neurotoxic effects in the brain. This hypothesis, however, has not been proved and is not universally accepted. One alternative concept is that cytokine release may stimulate new vessel formation, which contributes to capillary leakage.

Glial and white matter damage.—It has been shown that oligodendrocytes are extremely sensitive to radiation and that their destruction is associated with radiologic evidence of the demyelination that ensues (4,8). Although neurons are relatively insensitive to radiation, there is sufficient loss of cellular components, primarily in white matter, to account for the observed reduction in brain volume that accompanies central nervous system radiation toxicity. Documented metabolic changes that occur in irradiated cells—for example, reduced glycolysis—are associated with a decrease in glucose consumption, which correlates with the decrease in glucose and oxygen utilization observed on the positron emission tomographic scans obtained in patients with radiation-induced central nervous system necrosis (9).

Effects on the fibrinolytic enzyme system.—Sawaya (10) examined necrotic brain tissue samples obtained in patients with radiation-induced necrosis and found...
an absence of tissue plasminogen activator and an excess of urokinase plasminogen activator. These enzymes are members of a complex fibrinolytic pathway that has potent variable effects on blood vessels and brain tissue. Tissue plasminogen activator affects fibrinogen during blood clotting, whereas urokinase plasminogen activator is active in extracellular proteolysis. An increase in urokinase plasminogen activator with a concomitant decrease in tissue plasminogen activator may contribute to cytotoxic edema and tissue necrosis.

**Immune mechanisms.**—An intriguing concept, the validity of which is currently unknown, is the possibility of an immune response in the host secondary to tissue damage caused by radiation and chemotherapy. The potential role of autoimmune vasculitis in the response of the central nervous system to radiation-induced damage needs further investigation (8).

**Histopathologic Features**

The end point of radiation injury is necrosis that may develop months to years after the completion of radiation therapy and is frequently irreversible and often progressive (4,11). Radiation necrosis occurs most commonly around blood vessels within white matter (4,11). The most common histopathologic features are fibrinoid necrosis of blood vessel walls, with surrounding perivascular parenchymal coagulative necrosis (Fig 1). Extension and confluence of multiple perivascular foci of necrosis result in large serpiginous or “geographic” zones of parenchymal necrosis (Fig 1), which are followed by the deposition of mineral salts (ie, dystrophic calcification). An additional vascular lesion that is often observed consists of clusters of abnormally dilated, thin-walled telangiectasias (Fig 1c). Late vascular changes include vessel wall thickening caused by hyalinization, with resultant luminal narrowing (Fig 1b). White matter changes include focal and diffuse demyelination.

<table>
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<tr>
<th>Interval from completion of radiation therapy to histologically-verified necrosis in months</th>
<th>&quot;Pure&quot; radiation necrosis</th>
<th>Predominant radiation necrosis w/limited residual and/or recurrent tumor</th>
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<td>n = 20</td>
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**Radiologic Findings**

Several articles (12–26) on the imaging findings of adverse effects of therapeutic radiation to the brain have been published. Van Tassel et al (23) described MR findings of brain injury after accelerated fractionation radiation therapy combined with carboplatin chemotherapy for the treatment of malignant gliomas. The present study is an extension and expansion of that work, with emphasis on both the common and uncommon features of radiation necrosis of the brain.

**Radiation-induced necrosis of the white matter.**—Radiation-induced necrosis is the end result of perivascular coagulative necrosis affecting the white matter. As expected, radiation necrosis occurs most commonly at the site of maximum radiation delivery, that is, in the immediate vicinity of the tumor site and surrounding the surgical cavity of a partially or...
Radiation necrosis can closely resemble recurrent tumor at MR imaging or CT because of the following shared characteristics: (a) origin at or close to the original tumor site, (b) contrast enhancement, (c) growth over time, (d) edema, and (e) exertion of mass effect. With respect to the MR imaging characteristics of radiation necrosis, most lesions consist of an enhancing mass with a central area of necrosis. The contrast enhancement of these lesions is secondary to radiation-induced endothelial damage, which leads to the breakdown of the blood-brain barrier. The use of platinum-based chemotherapy drugs, such as cisplatin and carboplatin, combined with radiation therapy may contribute to the development of radiation-induced necrosis (27–30). On T2-weighted images, the solid portion of the radiation-induced necrotic mass has low signal intensity, and the central necrotic component shows increased signal intensity.

In addition to the most common pattern of radiation necrosis, which consists of a single lesion arising at the site of the original primary tumor, other less common patterns may also be observed. Examples include (a) multiple lesions, (b) lesions in the contralateral hemisphere, (c) lesions arising remotely from a primary cerebral site—for example, in the cerebellum (Fig 6) or brain stem, and (d) subependymal lesions. Each of these rarer patterns of radiation necrosis can be suggestive of a different pathologic process. For example, radiation necrosis occurring at the site of the resected primary tumor can be easily mistaken for recurrent tumor (Fig 1). Necrosis occurring distant to the primary site of tumor may mimic multifocal glioma (Fig 2). In Figure 3, the radiation necrosis around the periventricular white matter of the contralateral hemisphere simulating multicentric glioma has tumorlike associated edema and mass effect. Marks et al (2) described radiation necrosis arising contralaterally to the primary tumor site in one patient following whole-brain irradiation. In our series, we observed this finding in eight patients.

Multiple lesions can resemble multiple metastases (Fig 4a). The predilection for periventricular white matter involvement in radiation necrosis may, on rare occasion, mimic tumefactive multiple sclerosis (Fig 4b). The radiation necrosis that develops in the periventricular white matter may be explained by the fact that this neuroanatomic region has a relatively poor blood supply from long medullary arteries that lack collateral vessels and is therefore vulnerable to ischemic effects produced by postradiation vasculopathy (31,32). Therapy-induced necrotic lesions can also spread subependymally and mimic subependymal tumor spread (Fig 2b).

As radiation necrosis progresses with tumorlike growth, it can lead to severe shrinkage of the white matter and cortex and result in focal brain atrophy (Fig 5). The arcuate fibers in white matter are relatively resistant to radiation necrosis and are usually involved late in the disease process. An additional variant of radiation necrosis that warrants brief attention is the Swiss cheese pattern. This pattern can be visualized as a result of diffuse necrosis affecting the white matter and adjacent cortex. The Swiss cheese pattern reflects diffuse enhancements at the margins affecting the cortex and white matter, with intermixed foci of necrosis. Compared with lesions with the soap bubble pattern, Swiss cheese lesions are larger, more variable in size, and more diffuse (Fig 5).

The incidence of radiation necrosis after conventional therapy ranges from 5% to 24%, with higher rates at autopsy (2,33). In our series of 148 patients with treated malignant gliomas, pure radiation necrosis was observed in 20 (13.5%) patients, and a mixture of predominantly radiation necrosis intermingled with limited residual and/or recurrent tumor (less than 20% of resected tissue) was found in 16 (10.8%). It is important to remember that radiation-induced necrosis is a dynamic pathophysiologic process with several possible clinical outcomes. Although continued growth with atten-

**Figure 8.** Spontaneous regression of radiation-induced multifocal enhancement of the white matter that gradually disappeared within 29 months. Follow-up postcontrast transverse T1-weighted spin-echo image (500/11) obtained in a 41-year-old man who underwent surgery, accelerated radiation therapy, and chemotherapy for a nonenhancing anaplastic astrocytoma involving the left parietal lobe shows multilobular foci of radiation-induced enhancement (arrows) within the white matter.

**Figure 9.** Radiation-induced damage to the cortex simulating subacute infarction. Postcontrast transverse T1-weighted spin-echo image (500/11) obtained 17 months after therapy for an anaplastic astrocytoma involving the left cingulate gyrus shows an enhancing area (arrow) in the right insular cortex. This enhancing area was present on the follow-up MR image (not shown) obtained 1 year later.

**Figure 10.** Postcontrast transverse T1-weighted fat-suppressed spin-echo image (500/11) obtained in a 26-year-old man after surgery, 9 months after accelerated radiation therapy (55.5 Gy) and chemotherapy for a frontal lobe anaplastic astrocytoma, shows radiation necrosis involving the optic nerves (open arrows), chiasm (arrowheads), and tracts (solid arrows). The necrosis was confirmed at autopsy.
dant cytotoxic edema and mass effect is commonly seen, lethal progression is not inevitable in all cases. Some lesions will stabilize, and others will regress in size. Surgery may be required to reduce the mass effect and edema, and despite advancements in special imaging techniques, surgery may be needed to establish an accurate histopathologic diagnosis. Finally, despite the use of total gross resection, which includes removal of the necrotic tissue, radiation necrosis recurrence will be observed in some cases. It is anticipated that current efforts to further refine investigational radiographic techniques will lead to less ambiguous diagnoses of radiation-induced necrosis in the near future.

Radiation-induced enhancement of the white matter and cortex.—Radiation-induced enhancement, a milder form of brain injury, usually occurs within the white matter, can be single or multiple, and appears in varying sizes. This enhancement mostly affects the white matter at variable distances from the primary tumor site (Fig 8). The contralateral cerebral hemisphere or cerebellar white matter is affected less often. The pattern of enhancement can be nodular (Fig 8), linear (Fig 1), or curvilinear. These lesions are frequently seen at MR imaging and do not warrant biopsy if they remain stable (Fig 9) or regress (Fig 8) in size. However, progression to radiation necrosis should be suspected, and if they have an increase in size, accompanied by edema and mass effect (Fig 2). In such instances, surgery is recommended. Radiation-induced damage of this type can also occur within the cortex. For example, cortical gyral enhancement may simulate subacute infarction (Fig 9).

Radiation-induced necrosis of the cranial nerves.—Radiation-induced cranial neuropathy is relatively rare. Radiation-induced optic neuropathy (Fig 10) is likely to occur when focused radiation is delivered to tumors in the perioptic regions (34). The pathologic process of this neuropathy consists of optic pathway vasculopathy with secondary hemorrhage, reactive gliosis, necrosis, and atrophy. A similar process can occur around other cranial nerves, as demonstrated in a patient in our series with necrosis at and around the lateral lemniscus of the central auditory pathway (Fig 11).

In summary, the frequent diagnostic dilemma of recurrent neoplasm versus radiation necrosis is addressed in this study through a description of the varying spatial and temporal patterns of radiation necrosis that may be encountered at MR imaging:

1. If the tumor was a nonenhancing lesion before surgery and enhancing foci subsequently developed within and circumjacent to the tumor, the enhancing lesions often do not represent progression to a higher grade, but rather they are often the result of radiation necrosis.

2. If an enhancing focus develops at a distance from the primary glioma, radiation necrosis should be suspected; multiple enhancing areas do not necessarily represent multifocal glioma.

3. If an enhancing focus develops in the periventricular white matter, particularly capping the ventricles or within the corpus callosum, radiation necrosis should be suspected. The periventricular white matter is among the areas most susceptible to radiation necrosis.

4. Radiation necrosis should be suspected if a new enhancing lesion exhibits a soap bubble or Swiss cheese pattern.

The key point in any of these scenarios is that radiation necrosis should be included high in the differential diagnosis. It is important to recognize the spectrum of MR imaging features of radiation necrosis, because this tissue damage can mimic other pathologic processes.

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References


