Temporal characteristics of radiosurgical lesions in an animal model

DAVID R. BLATT, M.D., WILLIAM A. FRIEDMAN, M.D., FRANK J. BOVA, PH.D., DANIEL P. TEELE, D.V.M., AND J. PARKER MICKLE, M.D.

Departments of Neurological Surgery and Radiation Oncology, University of Florida College of Medicine, Gainesville, Florida

To characterize the temporal course of radiosurgical lesions, 19 cats were irradiated in an animal linear accelerator radiosurgical device. The animals were followed clinically and, at 3.5, 6, 12, 18, 23, 29, and 63 weeks, were studied with gadolinium-enhanced magnetic resonance (MR) imaging. They were then sacrificed after Evans blue dye perfusion, and gross pathological and histopathological studies were performed.

Mild neurological deficits developed between 3.5 and 4.5 weeks, correlating with the onset of mass effect both grossly and radiographically and with the maximum amount of white matter edema on T2-weighted MR imaging and microscopic examination. Clinical improvement occurred within several weeks as these resolved. The lesions were of similar size at all time intervals. Gadolinium-enhanced MR imaging demonstrated lesions with peripheral areas of enhancement and central nonenhancing regions which correlated histologically with areas of vascular proliferation and radiation necrosis, respectively. In the early lesions at 3.5 and 6 weeks, necrosis and edema were predominant. From 12 to 29 weeks, an intermediate stage was observed, with resorption of the necrotic debris as evidenced by progressive cavitation and microglial response and by increased perilesional vascularity. At 63 weeks, resorption was still taking place, but gliosis and diminution of the vascular response were seen.

KEY WORDS · animal model · linear accelerator · magnetic resonance imaging · radiation necrosis · stereotactic radiosurgery · cat

RADIOSURGERY is now a well-established treatment alternative for a variety of neurosurgical diseases, most notably arteriovenous malformations, acoustic schwannomas, and meningiomas. While its clinical use is increasing rapidly, the radiobiology of high-dose, small-volume, single-fraction irradiation remains poorly understood. Although a wealth of information is available regarding the biology of fractionated brain irradiation, the numerous differences between the two techniques render most of this knowledge inapplicable to radiosurgery. As there are few experimental studies of radiosurgery in the literature, the development of a reproducible animal model is crucial. Recently, we reported on the development of a device for animal radiosurgery and on the characterization of a dose-response curve for linear accelerator (LINAC) radiosurgery in a cat model. In that study, the radiobiological effects of a range of doses were studied at one time point (6 months post-irradiation) and histological and magnetic resonance (MR) imaging correlation were obtained. In the current experiment, one biologically effective dose was studied at multiple time points and the clinical, histological, and MR imaging changes were characterized.

Materials and Methods

Animal Radiosurgical Device

Nineteen adult cats, each weighing between 2.4 and 5.2 kg, underwent stereotactic irradiation using an animal radiosurgical device developed at the University of Florida. This device has been described in a previous publication. Briefly, it incorporates basic parts of the Kopf stereotactic frame for accurate target positioning. A motorized pendular movement of the device is used to describe a radiation arc, while the radiation source (either a LINAC or a cobalt machine) remains stationary. The pathway of the different radiation arcs is modified by rotation of the animal platform around the machine isocenter. Mechanical accuracy tests have shown a maximum alignment error of 0.15 mm.
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Fig. 1. Schematic drawing showing location of the target (cross) in the right internal capsule, with 84% (inner circle) and 42% (outer circle) isodose lines displayed. The treatment volume is the area inside the 84% isodose line. As is typical of linear accelerator radiosurgery, the radiation dose (125 Gy) was prescribed such that the center of the lesion received a dose not much higher than the periphery of the lesion (a homogeneous treatment).

Animal Preparation

This project was approved in advance by the Animal Use Committee of the University of Florida. Prior to irradiation, the 19 cats were anesthetized with a combination of subcutaneous xylazine (2 mg/kg) and intramuscular ketamine (10 mg/kg), orotracheally intubated, and attached to and restrained in the stereotactic frame. The cats also received subcutaneous atropine (4 mg/kg), penicillin (150,000 U), and antibiotic ointment in each ear. Supplemental anesthesia via isoflurane inhalation was delivered throughout the procedure.

Stereotactic Radiosurgery

The target for this experiment was located in the anterior limb of the right internal capsule. The specific coordinates were selected from a cat stereotactic atlas16 as follows (Fig. 1): anteroposterior, +19; lateral, right 7; and vertical, +6. This target is 3 mm inferior and 2 mm medial to that used in a prior experiment.17 In that study, no animal demonstrated any neurological deficit, and the edge of the lesions was too close to the dorsolateral cortical surface; therefore, the target was removed to a more central location for the current project. Each cat received 125 Gy of irradiation prescribed to the 84% isodose line and delivered through a 10-mm collimator via an 8-MeV LINAC machine (treatment volume 0.35 cc). This dose was chosen because it produced a consistent lesion in the prior study.17 One cat was anesthetized, fixed to the stereotactic frame, and ventilated but not irradiated to serve as a control.

Postirradiation Studies

Following irradiation, the animals were maintained and their neurological status monitored for variable lengths of time. Three cats each at 6, 12, 18, 23, and 29 weeks and two cats at 63 weeks postirradiation were anesthetized with intraperitoneal sodium pentobarbital (40 mg/kg), and coronal MR imaging of the brain was performed using a knee coil. In addition to unenhanced T1-weighted (TR 700 msec, TE 25 msec), T2-weighted (TR 3000 msec, TE 80 msec), and spin density (TR 3000 msec, TE 30 msec) images, studies were also obtained (TR 700 msec, TE 25 msec) after a bolus injection of 0.4 cc/kg of gadolinium-diethylenetriamine penta-acetic acid to assess blood-brain barrier breakdown. Immediately after MR imaging, while still maintained under deep general anesthesia, the animals were perfused intravenously with 5% Evans blue dye (1 cc/kg); they were subsequently killed with an overdose of intravenous pentobarbital, exanguinated, and perfused transcardially with pentobarbital and 4% paraformaldehyde. The brains were immediately removed and placed in 4% paraformaldehyde. Two cats were sacrificed at 3.5 weeks after the acute onset of a left hemiparesis; anorexia also developed in one. These animals were perfused with Evans blue dye and paraformaldehyde like the others, but MR imaging was not performed. The control animal was killed at 29 weeks as described above.

The brains were sliced in the coronal plane and the location, diameter, and macroscopic appearance of the lesions were examined and recorded. The sections containing the lesions were then embedded in paraffin and processed for histological analysis, which included staining with hematoxylin and eosin and Luxol fast blue for myelin. The histology was examined by an independent investigator (J.P.M.) for descriptive changes as well as quantification of areas of abnormality.

Results

Clinical Examination

All animals developed some neurological deficit, although this was mild in the majority of the cats and only one showed signs of distress. This cat and one other with a significant hemiparesis were sacrificed prematurely. No deficit or abnormal behavior was noted until 3.5 weeks after irradiation when the acute onset of a left hemiparesis developed in the above-mentioned two animals. This was dense in the one cat that appeared distressed and became anorectic; the other animal had a less severe deficit, with the hindlimb more severely affected. The following day nine other cats developed varying degrees of left hindlimb paresis, although none as severely as the first two; none of these showed any signs of distress. Within 1 week, five additional cats were affected and the remaining three animals developed similar deficits at 6, 7, and 14 weeks postirradiation. Trace to mild forelimb weakness developed in most of the animals. Improvement was observed in the majority of the cats over the following weeks, with mild spasticity developing at around 14 weeks. The control animal was neurologically intact.

Macroscopic Examination

Examination of coronal brain sections showed lesions characteristic for each sacrifice date and several...
Fig. 2. Representative coronal sections after Evans blue dye and paraformaldehyde perfusion (left) and corresponding gadolinium-enhanced magnetic resonance (MR) images (TR 700 msec, TE 25 msec) (right) in cats with radiosurgical lesions. A: At 3.5 weeks postirradiation, mass effect of midline shift and compression of the ipsilateral ventricle are seen. An area of softening, barely visible within the internal capsule, is surrounded by a thin ring of Evans blue stain. Hemorrhagic discoloration within the cortex and several engorged blood vessels are demonstrated. Magnetic resonance imaging was not performed at this time point. B: At 6 weeks, mild midline shift and ventricular compression are still evident. There is a clear necrotic lesion surrounded by a faint ring of Evans blue dye. The lesion involves predominantly white matter and is limited in its mediolateral diameter by the caudate nucleus and the cerebral cortex-claustrum. However, while the gray matter is not grossly necrotic, it is thinned when compared to the con-
tralateral side, suggesting tissue loss. C: An MR image at 6 weeks demonstrates a ring-enhancing lesion. D: At 12 weeks, there is no longer midline shift and the ipsilateral lateral ventricle is dilated. Necrosis is more pronounced and is surrounded by a ring of light Evans blue stain. The lesion remains primarily in the white matter but, as above, the ipsilateral caudate is clearly smaller. The white matter superior to the lesion appears abnormal. E: The MR image obtained at 12 weeks is similar in appearance to that obtained at 6 weeks, although the lesion extends more anteriorly into the frontal centrum and is more spherical as there is less surrounding gray matter. F: At 18 weeks, cavitation is beginning and the necrosis is more marked, although the size of the area of necrosis has remained relatively consistent. There is a ring of faint Evans blue dye surrounding the lesion and the area adjacent to the lesion is abnormal. Ewms blue stain. The lesion remains primarily in the white matter but, as above, the ipsilateral caudate is clearly smaller. The white matter superior to the lesion appears abnormal. G: Again, there is little change on MR images at 18 weeks. H: At 23 weeks, further ipsilateral ventricular dilatation is noted and there is a slight shift of midline to the side of the lesion. Cavitary necrosis is present, and the cortex and caudate adjacent to the lesion are thinned. Evans blue staining surrounds the lesion and extends into the white matter. I: Ipsilateral periventricular and mild meningeal enhancement is demonstrated on MR images obtained at 23 weeks. J: At 29 weeks, there is less white necrotic material as, presumably, resorption has taken place. The midline is shifted toward the lesion. There is dense Evans blue staining in a nearly diffuse pattern, as well as periventricular staining. Evidence of hemorrhage is present. K: The area of enhancement of the MR image at 29 weeks is similar in size to, but more irregular than, that at 23 weeks. The lesion enhances more diffusely in comparison to the ring enhancement demonstrated at earlier intervals. L: At 63 weeks, atrophy of the ipsilateral frontal lobe is seen, and Evans blue staining is present within and surrounding the lesion In this animal, no white necrotic material is demonstrated. Periventricular staining can be appreciated. M: A diffuse pattern of enhancement is shown on the MR image obtained at 63 weeks. Periventricular enhancement is marked.
<table>
<thead>
<tr>
<th>Time of Sacrifice (wks)</th>
<th>Mass Effect</th>
<th>Macrocopic Findings</th>
<th>Microscopic Findings</th>
<th>Magnetic Resonance Imaging Findings</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>T₁-Weighted</td>
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<tr>
<td>3.5</td>
<td>midline shift, ventricular compression</td>
<td>softening in white matter; no clear necrosis; cortex with hemorrhage vs. necrosis; scattered petechiae vs. dilated or thrombosed vessels</td>
<td>early necrosis, edema, minimal cavitation, punctate hemorrhages, hypervascularity</td>
<td>not done</td>
</tr>
<tr>
<td>6</td>
<td>midline shift, ventricular compression</td>
<td>necrosis without cavitation; gray matter discolored, possible edema but no necrosis</td>
<td>edema, necrosis with small central cavitation, perivascular cuffing</td>
<td>slightly decreased signal</td>
</tr>
<tr>
<td>12</td>
<td>ipsilateral ventricular dilatation</td>
<td>necrosis more pronounced; gray matter probably involved, but less than white matter</td>
<td>cavitation, hypervascular, less edema, cortex &amp; ependyma involved</td>
<td>decreased signal</td>
</tr>
<tr>
<td>18</td>
<td>ipsilateral ventricular dilatation</td>
<td>cavitation beginning; gray matter definitely involved but still predominantly a white matter lesion</td>
<td>cavitation, less edema, hemorrhage, hypervascular, cortex &amp; ependyma involved</td>
<td>significantly decreased signal</td>
</tr>
<tr>
<td>23</td>
<td>ipsilateral ventricular dilatation</td>
<td>cavitation more pronounced</td>
<td>sharply demarcated cavity, less edema, hemorrhage, increased subependymal &amp; pial vascularity, perivascular cuffing</td>
<td>significantly decreased signal</td>
</tr>
<tr>
<td>29</td>
<td>same with slight shift to side of lesion</td>
<td>much less necrotic material than in prior groups; cavitation; more hemorrhage than at other intervals</td>
<td>hemorrhage, hemosiderin, very vascular, cavitation contracted</td>
<td>significantly decreased signal</td>
</tr>
<tr>
<td>63</td>
<td>same as at 29 wks</td>
<td>less necrotic material; frontal atrophy; cavitation in one of two brains</td>
<td>slightly less vascular, mild astrocytosis, no hemorrhage</td>
<td>decreased signal</td>
</tr>
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Table 1: Pathological and radiological findings in cats with radiosurgical lesions

Types of abnormalities that progressed with time (Table 1). Mass effect with midline shift and compression of the ipsilateral ventricle were seen in the brain studies at 3.5 and 6 weeks. The brains studied at later time points showed no mass effect. In fact, progressive ipsilateral ventricular dilatation consistent with a loss of brain matter was seen.

The brains studied at 3.5 weeks postirradiation showed a focal area of softening in the white matter that was suggestive of early necrosis (Fig. 2A). There were several engorged or thrombosed blood vessels scattered within or immediately adjacent to this area. Areas of yellowish discoloration confined to the cortical region abutted the lesion. This abnormality followed the cortex from the gyral surface into the depths of the sulci. With the exception of several of the above-mentioned engorged or thrombosed blood vessels, the caudate and other subcortical gray matter appeared uninvolved. There was a faint ring of Evans blue stain around the area of softening extending into the surrounding white matter in one of the two brains studied.

The second showed no staining, but an area of abnormality was demonstrated around the lesion, suggestive of edema and similar in size to the area of staining in the first animal.

At 6 weeks, the lesions in the three brains examined appeared as sharply demarcated areas of white discoloration, clearly suggestive of necrosis (Fig. 2B). There was no cavitation. The necrotic area appeared to be confined to white matter, but the surrounding gray matter was discolored and the caudate was smaller than on the contralateral side. Two brains demonstrated a ring of Evans blue stain surrounding the lesion, while the other displayed an area of abnormality suggestive of edema. In all cases the staining or edema extended further into the surrounding white matter than into the gray matter.

In the three brains examined at 12 weeks, the white necrotic region was more pronounced, still sharply demarcated from the surrounding brain, and without cavi-
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![Figure 3: Scatterplot demonstrating correlation in size between areas of central nonenhancement on magnetic resonance imaging (diamonds) and necrosis on macroscopic examination (squares).](image)

![Figure 4: Scatterplot demonstrating correlation in size between areas of gadolinium enhancement on magnetic resonance imaging (diamonds) and Evans blue staining or edema on macroscopic examination (squares).](image)

...tation (Fig. 2D). Gray matter at the edges of the lesion was clearly necrotic, but seemingly to a lesser extent than the white matter. Atrophy of the ipsilateral caudate nucleus had progressed. All three brains had evidence of apparent hemorrhage and a faint ring of Evans blue stain surrounding the lesion which, as in the previous brains studied, was thicker where the lesion bordered white matter.

The brains studied at 18 weeks (Fig. 2F) and 23 weeks (Fig. 2H) showed continued progression of the necrotic process. Cavitation was first seen at 18 weeks and well-formed cavities were present by 23 weeks. The lesion still seemed to involve predominantly the white matter, but the borders of the gray matter were definitely necrotic. Hemorrhage was evident in several brains. Evans blue staining was similar to that described at 12 weeks, but at 23 weeks the stain was more intense than previously demonstrated. All three brains examined at the 23-week time point showed a thicker ring of stain extending into the surrounding white matter.

At 29 weeks, the amount of white necrotic material had diminished significantly (Fig. 2J). Apparently, resorption of necrotic debris and contraction of the lesion were taking place. Cavitation and loss of surrounding gray matter had progressed further. Hemorrhage was present in all three brains studied, and in one brain an area that appeared to be hemorrhagic discoloration extended into the frontal white matter. Evans blue staining was much more intense, forming a thick irregular ring; the staining was nearly diffuse in one brain. Staining was also seen in the surrounding white matter, extending into the frontal white matter in two of the three brains examined.

At 63 weeks, one brain showed neither cavitation nor any white necrotic material, but instead demonstrated a central area stained a blue-brown color (Fig. 2L). The other animal sacrificed at this time point had a cavitary lesion with some necrotic debris remaining. Both brains displayed significant atrophy of the ipsilateral frontal lobe, and a thick ring of Evans blue dye. Ipsilateral periventricular Evans blue staining was present and extended well posterior to the lesion.

The areas of softening or necrosis were of similar size at all time points until 29 and 63 weeks, when apparent resorption of necrotic debris had taken place (Fig. 3). The maximum diameter of the lesions ranged from 8 to 10 mm in a superoinferior orientation, while the smaller diameter ranged from 5 to 8 mm in the mediolateral direction. The lesions were located in the anterior limb of the internal capsule and seemed limited in their mediolateral extent by the caudate nucleus and the claustrum, respectively, as gray matter did not appear to develop the same level of necrosis as white matter. The lesions tended to be slightly larger at longer intervals postirradiation since softening in surrounding gray matter took longer to develop. Lesions more anteriorly located tended to be larger, especially in the mediolateral extent, as they apparently were not as limited by subcortical gray matter.

All areas of apparent softening or necrosis were surrounded by either a ring of Evans blue stain or a similar region of abnormal-appearing brain. The maximum diameters of the areas ranged from 10 to 14 mm in a superoinferior orientation, while the smaller diameter ranged from 7 to 11 mm in the mediolateral direction (Fig. 4). This rim of stain or abnormal-appearing tissue surrounding the necrotic lesion was thicker where it involved white matter.

The fact that the Evans blue staining was inconsistent and lighter at the earlier intervals postirradiation is of questionable significance as staining of the choroid plexus was also lighter in these brains. It is possible that the stain washed out while the specimens were being stored in paraformaldehyde or that the Evans blue dye used in the earlier animals was of different quality.
This method of utilization of Evans blue dye in vivo serves as a purely qualitative, not quantitative, analytical dye.

**Magnetic Resonance Imaging**

Magnetic resonance images showed the same mass effect and atrophic changes as the pathological studies of the coronal brain sections (Table I). Images were consistent at each postirradiation interval, with the T₁-weighted sequences demonstrating a progressive decrease in signal in the area of the lesion related to time from the date of irradiation. The size of this low-signal area was relatively constant (Fig. 5 left). The T₂-weighted images showed a variety of changes depending on the time since irradiation. At 6 weeks, increased signal was seen throughout the entire frontoparietal and temporal white matter in all three brains studied, while the target demonstrated a lower signal (Fig. 5 right). At 12 weeks, images in two of the three animals still showed this white matter change, but it was less pronounced; white matter appeared normal in the third brain image. At this time point, the target area showed increased signal in all three cats. At 18 and 23 weeks, all images demonstrated high-signal lesions with low-signal centers. Only one animal showed surrounding white matter abnormalities at 18 weeks, which was limited to the frontal lobe. At 29 weeks, the lesions appeared as a high signal with smaller areas of low signal in the center. All three brains examined at this time point showed increased signal in the frontal white matter. At 63 weeks, there were focal areas of increased signal in the lesion, with one lesion showing a low-signal center. Spin-density sequences provided no additional information relative to that evident on the T₂-weighted images.

Gadolinium-enhanced MR images were the most sensitive in demonstrating the radiation-induced abnormalities. All animals had consistent ring-enhancing lesions (Fig. 2C, E, G, and I) except at 29 and 63 weeks, when the enhancement was more irregular and nearly diffuse (Fig. 2K and M). The size and appearance of the central areas of the lesions that did not enhance with gadolinium correlated well with areas of apparent necrosis of macroscopic specimens (Fig. 3). The diameter and appearance of the area of gadolinium enhancement matched the area of Evans blue stain or abnormal-appearing brain surrounding the lesion (Fig. 4). The areas that enhanced were not necrotic; as demonstrated histologically (see below), they represented a surrounding region of edema and vascular proliferation. Several of the brains showed ipsilateral periventricular enhancement. This was more prominent at longer intervals postirradiation and was seen in all five animals studied at 29 and 63 weeks. Meningeal enhancement was also seen in images obtained at 23, 29, and 63 weeks. Magnetic resonance imaging data will be discussed in detail in a separate publication.

**Microscopic Examination**

Sharply demarcated lesions were seen in brain specimens obtained at all time points (Table I). These lesions consisted of a central area of necrosis that progressed with time, showing increasing amounts of cavitation surrounded by an area of edema and vascular proliferation.

The lesions at 3.5 weeks demonstrated edema, demyelination, axonal loss, and neuronal death (Fig. 6 upper left). There was a thin rim of perilesional demyelination that was not observed in specimens from later intervals. Coagulative necrosis without cavitation was present, as well as engorged blood vessels and microhemorrhages in the surrounding area. Further necrosis was seen at 6 weeks. Surrounding edema was most marked at 3.5 and 6 weeks, corresponding with the midline shift and neurological deficits seen at these time points. In these animals, edema was nearly pan-hemispheric, extending well into the deep white matter of the parietal lobe. This edema, both locally and distant, decreased progressively with time, completely dissipating at later intervals.

Cavitation was evident at 12 weeks (Fig. 6 upper right) and, by 23 weeks, a sharply demarcated cavity was seen. At 29 weeks, contraction or shrinkage of the necrotic lesion was noted (Fig. 6 lower left). The cavitation appeared to result from a mobilization of phagocytes that paralleled the progressive ingrowth of small arteries and arterioles in a hypervascular pattern around the periphery of the necrosis. Continued vascular proliferation was correlated with some hemorrhage in the hypervascular region and into the cavity as well. Progressive amounts of hemorrhage were evident through 29 weeks, mostly proximal to the areas of neovascularity.

At 63 weeks, the hypervascularity was slightly decreased, while a mild astrocytosis was present in the peripheral zone (Fig. 6 lower left). No hemorrhage was seen in the two brains studied at this time point.

The area of necrosis correlated in size and shape with the central nonenhancing region on MR images, while the area of vascular proliferation matched the ring of enhancement. Increased signal on T₂-weighted MR images in the white matter outside the lesion correlated with edema. At later postirradiation intervals when there was no change distant from the lesion on T₂-weighted images, the brain was normal.
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None of the specimens showed any calcification, endothelial proliferation, or vascular fibrinoid necrosis. Astrocytosis was seen only at 63 weeks and was mild. Gray and white matter were equally affected when included within the lesion. Several specimens showed perivascular cuffing. The ependymal surface of the ipsilateral ventricle showed progressive disruption and subependymal hypervascularity, which was first noted at 12 weeks. There was increased pial vascularity at later time points.

Discussion

Relatively little information has been published regarding the full temporal course of radiosurgical lesions. The literature that does exist is very heterogeneous due to numerous variables, including dosage, treatment volume, follow-up review, terminology, and species (Table 2).

FIG. 6. Representative histological sections of cats with radiosurgical lesions. H & E, ×2.2. Upper Left: At 3.5 weeks postirradiation, a central area with dying neurons and marked edema (E) with a surrounding area of vascular engorgement and microhemorrhages (arrow) is seen. Edema is also present in the surrounding normal brain (B). Upper Right: At 12 weeks, coagulative necrosis (N) with early cavitation and a microglial response are seen. A zone of neovascularity (V) surrounds the necrotic center and there is sharp demarcation from surrounding brain. Lower Left: At 29 weeks, recent and old hemorrhage (H) in the necrotic region is seen, especially adjacent to the area of hypervascularity (V). The lesion is sharply demarcated from normal brain. Lower Right: At 63 weeks, a well-formed cavity (C) is present as well as a reduction in the amount of perilesional hypervascularity (V) and a mild gliosis. The lesion remains sharply demarcated from normal brain.

Early glial scar formation, and development of a surrounding rim of vascular proliferation; and 3) a late stage characterized by a predominant glial scar. A summary of the literature, presented in Table 2, separates the data into these early, intermediate, and late stages based upon pathological findings. Human and animal results are grouped together and studies that evaluate lesions at more than one time point are placed in the category into which most of the data falls.

In the early stages of development of radiosurgical lesions, the first abnormality seen microscopically seems to be a central area of edema. This is followed by the development of coagulative necrosis associated with perilesional edema, demyelination, vascular proliferation, microhemorrhages, and dilated vessels with clumping of red blood cells. Lesions in the intermediate stage demonstrate progressive cavitation secondary to a macrophagic or microglial response. Hemorrhage seems common and is likely related to the ongoing capillary proliferation surrounding the necrotic center of the lesion. Mild gliosis may be present. The late phase is characterized by a glial scar without hypervascularity.

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<th>Authors &amp; Year</th>
<th>Method of Radiation</th>
<th>Subject</th>
<th>No. Studied</th>
<th>Radiation Dosage (Gy)</th>
<th>Time of Study</th>
<th>Results of Study</th>
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<tr>
<td>Leksell, et al., 1990</td>
<td>proton beam</td>
<td>goat</td>
<td>4</td>
<td>200–380</td>
<td>1, 4 mos</td>
<td>discrete necrotic lesions at 1 &amp; 4 mos in animals receiving 200 Gy; perivascular hemorrhages; perivascular cuffing, distended thin-walled vessels at margin of lesion, a few macrophages at 4 mos</td>
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<td>Larson, et al., 1990</td>
<td>proton beam</td>
<td>human</td>
<td>1</td>
<td>200</td>
<td>62 days</td>
<td>sharply demarcated necrotic lesion; small hemorrhages in center of lesion near vessels with necrotic walls &amp; at periphery associated with vessels with small caliber &amp; collagenous walls</td>
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<tr>
<td>Kjellberg, et al., 1994</td>
<td>Bragg peak</td>
<td>monkey</td>
<td>?</td>
<td>240</td>
<td>20 days</td>
<td>sharply demarcated lesion with central zone coagulative necrosis; thin transitional zone with dilated vessels, clumped &amp; extravasated red blood cells</td>
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<td>Hecht-Leavitt, et al., 1987</td>
<td>LINAC</td>
<td>cat</td>
<td>6</td>
<td>35</td>
<td>7, 8 mos</td>
<td>MRI at 4 to 6-wk intervals; in one cat, change on T2-weighted MRI at 7 mos corresponding to inflammation, demyelination, reactive astrocytosis; in one cat, necrosis, vascular proliferation at 8 mos after gadolinium enhancement; MRI normal in other cats</td>
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<td>Autscheler, et al., 1990</td>
<td>gamma knife</td>
<td>baboon</td>
<td>11</td>
<td>20–150</td>
<td>2 mos</td>
<td>increased signal on T2-weighted MRI within target volume in animals receiving 150 Gy</td>
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<tr>
<td>Lunsford, et al., 1990</td>
<td>gamma knife</td>
<td>baboon</td>
<td>3</td>
<td>150</td>
<td>6, 24 wks</td>
<td>no radiographic changes at 4 wks; contrast-enhancing lesions at 6, 8, 24 wks; demyelination, perilesional edema, microhemorrhage, astrocytosis, widened perivascular spaces, but no necrosis at 6 wks; necrosis, astrocytosis, calcification at 24 wks</td>
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<tr>
<td>Statham, et al., 1990</td>
<td>gamma knife</td>
<td>human</td>
<td>1</td>
<td>25</td>
<td>13 mos</td>
<td>irregular ring-enhancing mass with white matter edema &amp; midline shift on CT; biopsy showed necrosis with endothelial proliferation, perivascular cuffing, fibrinoid necrosis, enhanced vascularity, intramedullary thrombus</td>
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<td>Lo, et al., 1991</td>
<td>Bragg peak</td>
<td>rabbit</td>
<td>16</td>
<td>15, 30</td>
<td>8–20 mos</td>
<td>with 30 GyE all developed radiographic changes from 9 to 11 mos; increased white matter signal on T2-weighted MRI; focal enhancement after gadolinium infusion; edema, demyelination, focal areas of necrosis, reactive astrocytosis, microglia, dilated blood vessels</td>
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<tr>
<td>Kondziolka, et al., 1992</td>
<td>gamma knife</td>
<td>rat</td>
<td>?</td>
<td>200</td>
<td>1, 7, 14, 21, 30, 60 days</td>
<td>no abnormality at 1 &amp; 7 days; central edema at 14 days; necrosis at 21 days; lesion slightly larger at longer intervals; arteriolar wall thickening, astrocytosis, edema present in 1–2 mm surrounding area of necrosis</td>
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<td><strong>intermediate stage</strong></td>
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<td>Rexed, et al., 1959</td>
<td>proton beam</td>
<td>rabbit</td>
<td>20</td>
<td>200</td>
<td>2–56 wks</td>
<td>slightly larger lesions at later intervals; neuronal loss, demyelination, axonal degeneration, small perivascular hemorrhages at 2 wks; progression with vascular congestion, edema at 4 wks; cavitation first seen at 10 wks; capillary proliferation with hemorrhage at 23 wks</td>
</tr>
<tr>
<td>Wenerstrand &amp; Ungerstedt, 1970</td>
<td>gamma knife</td>
<td>human</td>
<td>12</td>
<td>18–25</td>
<td>3 wks–7.5 mos</td>
<td>“fairly uniform” lesions; necrotic with thrombosed necrotic vessels; occasional hemorrhage; macrophages in lesions older than 3 wks; surrounding zone with increased vascularity; perivascular cuffing &amp; slight astrocytic proliferation</td>
</tr>
<tr>
<td>Steiner, et al., 1980</td>
<td>gamma knife</td>
<td>human</td>
<td>21</td>
<td>10–25</td>
<td>3 wks–400 days</td>
<td>lesion at 400 days with macrophages, calcifications, a few multinucleated giant cells, slight astrocytic proliferation in wall necrotic area; no lesions with doses &lt; 14 Gy</td>
</tr>
<tr>
<td>Spiegelmann, et al., 1993</td>
<td>LINAC</td>
<td>cat</td>
<td>15</td>
<td>50–150</td>
<td>6 mos</td>
<td>low-dose lesions with areas of edema, demyelination, reactive gliosis, vascular proliferation; high-dose lesions with increasing amounts of hemorrhage &amp; necrosis; gadolinium enhancement on MRI correlated with areas of blood-brain barrier breakdown demonstrated by Evans blue staining</td>
</tr>
<tr>
<td><strong>late stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson, et al., 1979</td>
<td>proton beam</td>
<td>goat</td>
<td>6</td>
<td>200</td>
<td>1.5–4 yrs</td>
<td>necrotic cavity surrounded by margin with calcifications, perivascular cuffing, macrophages, astrocytosis at 18–28 mos; increased vascularity at 18 mos; endothelial proliferation at 25 &amp; 26 mos; glial scar first seen at 26 mos &amp; prominent at 39 &amp; 48 mos</td>
</tr>
</tbody>
</table>

* For an explanation of stages, see Discussion. LINAC = linear accelerator; MRI = magnetic resonance image; CT = computerized tomography.

† This case was also reported by Mair, et al.14
Temporal characteristics of radiosurgical lesions

The present study is one of the few animal studies to fully explore the temporal characteristics of radiosurgical lesions and to correlate the pathology with MR imaging and clinical findings. Lesions in the early stage (at 3.5 and 6 weeks) demonstrated necrosis, edema, and mass effect. The onset of clinical symptoms occurred at this time, when mass effect was present both grossly and radiographically. This correlated with the maximum amount of white matter edema on T2-weighted MR images and microscopic examination. Clinical improvement occurred as the edema resolved. Resolution of necrotic debris, as evidenced by progressive cavi
tation and phagocytic response, and increased perilesional vascularity occurred during the intermediate stage (12 to 29 weeks). Gd-DTPA-enhanced imaging identified peripheral areas of blood-brain barrier breakdown and central areas of enhancement that correlated with areas of hypervascula
rity and radiation necrosis, respectively. The 63-week interval seemed to represent a transition zone to the late stage when resorption was still taking place, but gliosis and diminution of the vascular response were beginning. It is likely that brains examined at a time further from the date of irradiation would show a more pronounced glial response.

This model produced consistent radiosurgical lesions at each time interval. Moreover, it provides clinical, radiographic, and pathological correlation. Future research utilizing this model could investigate the importance of dose homogeneity, radiosensitizers, protective agents, and the tolerance of specific brain structures.

References


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Address reprint requests to: William A. Friedman, M.D., Department of Neurological Surgery, Box J-265, H. H. W. Health Center, University of Florida, Gainesville, Florida 32610.