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CLINICAL-RADIOLOGICAL EVALUATION
OF SEQUELAE OF STEREOTACTIC
RADIOSURGERY FOR INTRACRANIAL
ARTERIOVENOUS MALFORMATIONS

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INTRODUCTION

Stereotactic heavy-charged-particle Bragg peak radiosurgery has been used to treat 322 patients with surgically-inaccessible intracranial vascular malformations. (The clinical results of this method for the treatment of angiographically demonstrable arteriovenous malformations (AVMs) and angiographically occult vascular malformations (AOVMs) of the brain are described in separate reports of this symposium). The great majority of patients have had an uneventful post-treatment course with satisfactory health outcomes [5,9]. However, several categories of delayed sequelae of stereotactic radiosurgery have been identified, involving the vascular structures essential for the integrity of the brain tissue and the brain parenchyma directly [5,7,9]. These categories reflect both reaction to injury and to alterations in regional hemodynamic status, and include vasogenic edema, occlusion of functional vasculature, radiation necrosis, and local or remote effects on cerebral arterial aneurysms.

METHOD

The method of stereotactic heavy-charged-particle Bragg peak radiosurgery for the treatment of intracranial vascular disorders has been described previously [1,2,5]. (The treatment planning procedure is described in a separate report of this symposium). Patients are examined on a regular follow-up basis. Cerebral angiography is
performed at 12-mo intervals until the AVM has been completely obliterated, or has stabilized. MRI scanning is performed at 6-mo intervals, in order to assess the vascular response and to identify early or delayed radiation injury and/or edema in the brain, and to guide appropriate management. Patients with AOVMs are followed by MRI scanning at 6-mo intervals; follow-up angiography is not performed.

RESULTS AND DISCUSSION

Acute Sequelae

No procedure-related nausea, vomiting or headaches occurred after radiosurgery in any AVM or AOVM patients treated with heavy-charged-particle radiosurgery. Three patients with a pre-existing history of seizures experienced focal or generalized seizures within 24 hours of treatment, but all quickly returned to normal. There has been no other immediate morbidity from the treatment, and no deaths have occurred from the irradiation procedure.

Delayed Sequelae: Direct Effects

The incidence of delayed sequelae in the 322 AVM and AOVM patients in this series treated with heavy-charged-particle Bragg peak radiosurgery is listed in Table 1.

Vasogenic edema. Asymptomatic edema develops primarily in the deep white matter in about 20% of AVM patients treated with high-dose single-fraction Bragg peak helium-ion radiosurgery. Radiologically, a high intensity signal is found on an MRI scan (Figures 1 and 2), or a region of low attenuation on a CT scan. This process tends to occur when the treatment volume is deep within the white matter [5,7], and appears to be a consequence of the relatively looser cellular packing in the white matter which permits a less restricted diffusion of water into the surrounding tissue. Its underlying mechanism is not well understood, but it may be associated with delayed injury to the endothelial lining with loss of integrity of the intimal boundary and with concomitant plasma transudation into the brain parenchyma. Most often the process is contained in an immediate 2-to-3 mm shell surrounding the irradiated target, and even extensive regions of white matter edema may be present without any clinical manifestations (Figures 1 and 2). Deep white matter edema becomes demonstrable at about 12 to 18 mo after irradiation, persists as a limited process or extends over the next 12 to 18 mo, and then begins to regress without treatment; sequential MRI studies in asymptomatic patients demonstrate that complete regression to normal brain architecture occurs after as long as 3 y (Figure 2).

If the edema is massive or present in central brain loci, reversible or irreversible neurologic dysfunction may result due to mass effect or impaired local metabolism (Figure 3). Symptomatic edema has developed in about 8% of irradiated patients;
about half of these cases are only minimally or transiently symptomatic, and most respond quickly to prompt corticosteroid therapy. The process appears to be dose- and volume-dependent, but not always, and symptoms, in large measure, depend on the site in which the edema occurs (Figure 3).

**Arterial occlusion.** Occlusion of functional arterial vessels immediately adjacent to or hidden within the AVM, and associated with regional cerebral infarction, can be a serious clinical problem if it occurs; however, this is an infrequent event. Obliteration of abnormal AVM arterial vessels occurs with regularity, but the normal arterial vasculature within the treatment field, though irradiated to high doses, appears to be considerably more resistant to obliterative changes. Furthermore, the presence of collateral circulation may prevent this potential complication from becoming clinically symptomatic more often than the observed 2 to 3% incidence. Symptomatic arterial occlusion may develop as early as 8 mo and as late as 27 mo after radiosurgery [5,7]; this process is also dose- and volume-dependent, and most often, mild and transient in nature. Generally, it is diagnosed by the development of neurologic changes referable to the irradiated region, and in the absence of edema on MRI or CT scans (Figure 4). Frequently, angiographic evaluation demonstrates complete obliteration of the AVM and fails to reveal any irregular narrowing in the intact arterial system; subacute small vessel occlusion is the apparent mechanism of injury. However, angiographically demonstrable radiation-associated vasculopathy with concomitant infarction with severe neurologic deficit as late sequelae has been observed (Figure 5) [7].

**Venous thrombosis.** Thrombosis of draining veins occurred infrequently after irradiation. Stereotactic heavy-charged-particle radiosurgery is planned to exclude, to the extent possible, the venous structures of the AVM, because the venous component is considered to represent a passive sink, even in high-volume, high-flow AVMs. Additionally, veins are much less sensitive than arteries to irradiation-induced vascular obliteration [4].

**Radiation necrosis.** Delayed radiation necrosis has been confirmed histologically in two patients (Figure 6). Additional cases may have occurred within the “symptomatic vasogenic edema” group of patients who responded variably to corticosteroid therapy or within the “asymptomatic edema” group when injury was limited to a relatively silent region of the brain. The effect appears, in general, to be dependent on dose and volume treated, but injury has occurred at doses well below that of the earlier high-dose treatment group in this series. The extent to which the effect is symptomatic depends on the region of the brain affected; small volumes in “silent” regions can be damaged with little neurologic sequelae. The overall incidence of symptomatic necrosis in our series is about 1% after doses in the range of 45 to 25 GyE delivered acutely; necrosis has not been observed below 25 GyE delivered acutely, in 1 or 2 fractions, even when relatively large volumes of brain parenchyma are irradiated.
Delayed Sequelae: Indirect Effects

Aneurysms. Aneurysms are associated with intracranial AVMs, and the incidence of aneurysms among untreated AVM patients has been estimated variably at 3 to 9% [6]. Often it is not possible to determine whether an intracranial hemorrhage occurs from an AVM or from an associated aneurysm. The cerebral angiograms of all AVM patients who are candidates for stereotactic radiosurgery should be examined for the presence of arterial aneurysms. Stereotactic radiosurgery is not an effective treatment for aneurysms; these should be treated by surgical or neuroradiologic procedures [10]. The followup cerebral angiograms of all patients after stereotactic radiosurgery also must be evaluated carefully for the de novo appearance of arterial aneurysms or evidence of enlargement of any previously demonstrated aneurysms.

A 32-y-old woman sustained a subarachnoid hemorrhage from a ruptured aneurysm of the basilar artery tip 10 mo after stereotactic radiosurgery (dose, 25 GyE) of a very large (24,000 mm$^3$) high-flow left parietal AVM fed by branches of the left middle cerebral artery. The aneurysm had not been demonstrated on carotid or vertebral artery angiography at the time of radiosurgery, but apparently enlarged and ruptured after radiosurgery had induced a near-complete obliteration of the AVM. The aneurysm was not in the radiation field and was not directly associated with the feeding vessels of the AVM. It appears the resulting increase in the regional cerebral vascular resistance was transmitted to the vertebral artery branches, and this hemodynamic change was sufficient to induce expansion and hemorrhage from the previously dormant aneurysm. The aneurysm was surgically clipped, the AVM went on to complete obliteration within the next several months, and the patient made a full recovery.

A 21-y-old man with a 6,000 mm$^3$ left parietal AVM hemorrhaged 9 mo after stereotactic radiosurgery (dose, 28 GyE) from a sausage-shaped pseudoaneurysm that apparently formed from the dissection of a portion of the vascular media of the AVM. This was surgically wrapped, and the AVM went on to complete obliteration within the next year. The patient has had some right-sided spasticity and increased difficulty with seizure control since the hemorrhage.

An 11-y-old boy with a large (14,000 mm$^3$) left thalamic AVM hemorrhaged 16 mo after stereotactic radiosurgery (dose, 25 GyE) from an aneurysm that had previously been hidden within the dense cluster of AVM shunting vessels. After the AVM had been partially obliterated in response to radiosurgery, an aneurysm was readily identified within the core of the AVM. The patient recovered rapidly from the hemorrhage, and the aneurysm was subsequently occluded by balloon embolization.

Partial-volume irradiation response. The creation of high-flow shunting within an AVM may increase the likelihood of subsequent intracranial hemorrhage; this is a potential hazard of treatment that obliterates only a portion of an AVM, such as
flow-directed embolization, subtotal surgical resection or limited focal irradiation. High-flow, high-volume shunting of blood flow within the AVM can be created when a radiosurgical treatment targets only the earliest component of the arterial phase, or the so-called feeding “nidus”, rather than the entire arterial phase, for vascular obliteration [5]. When the entire arterial phase of the AVM has been included in the radiosurgical field, the incidence of complete AVM obliteration 2 y post-treatment for all volumes up to 60,000 mm$^3$ is approximately 85%. However, in a subset of patients where radiosurgery was intentionally narrowed-down and limited to the earliest-filling arterial nidus in order to protect normal brain tissue, many had an incomplete response of vascular obliteration. In these cases, we frequently observed complete obliteration confined to the radiosurgically-treated target volume, but persistence of an undesirable shunt in the unirradiated periphery of the lesion, and retreatment was required (Figure 7). Therefore, we do not consider acceptable any radiosurgery treatment plan that fails to encompass the entire arterial phase of the AVM in a uniformly-distributed radiation field [5].

Current Clinical Research

The presence of an intracranial AVM alters the cerebral blood flow dynamics, perturbing the cerebral perfusion in the immediate region, and generally throughout the brain [8]. The brain tissue immediately surrounding an AVM (or intertwined within it) cannot be considered as normal tissue. These regions may have been subject to insult from ischemia, prior hemorrhage, partial surgical resection or flow-directed embolization, or previous large field radiation therapy. Impaired local perfusion with a concomitant vascular steal phenomenon is commonly present, with considerable diminution of oxygenation and nutrition to the regional brain tissue, and accumulation of metabolic waste products.

Clinical research protocols utilizing positron emission tomography (PET) scanning are in progress in our program at Lawrence Berkeley Laboratory to characterize pathophysiologic changes in regional cerebral blood flow ($^{122}$I-HIPDM), glucose metabolism ($^{18}$F-fluoro-deoxyglucose) and blood-brain barrier integrity ($^{82}$Rb) in response to stereotactic heavy-charged-particle radiosurgery of inoperable intracranial AVMs. These changes are correlated with sequential MRI scans. Preliminary PET studies have demonstrated improvement in cerebral blood flow and metabolism after reversal of vascular steal and redistribution of blood flow following heavy-charged-particle radiosurgery. We have also observed selected cases of impaired blood-brain barrier integrity as a late consequence of charged-particle radiation; this has been demonstrated in asymptomatic patients following complete obliteration of their AVMs.

CONCLUSIONS

We have presented in this report the clinical and radiologic sequelae observed
in our series of 322 patients with inoperable intracranial vascular malformations treated with stereotactic heavy-charged-particle radiosurgery at Lawrence Berkeley Laboratory. We consider any definite or possible symptomatic sequelae of treatment to be complications, even if functional impairment is minimal or temporary. Many of these reported sequelae could be considered to be minor or an acceptable trade-off for the cure of an inoperable life-threatening condition. We believe that all possible adverse consequences of treatment should be reported, even though it may not be possible to ascertain whether clinical worsening in a given patient is the result of interventional therapy or a manifestation of the natural history of the disorder. Some untreated individuals can be expected to experience neurologic deterioration, for example, as a consequence of progressive vascular steal or an undetected hemorrhage. The complications encountered in this series, even though scored very conservatively, compare favorably with the potential risks of surgically-accessible AVMs or the spontaneous risk of progressive neurologic deficit in this patient group [3].

The direct and indirect sequelae identified in this report are to be expected as a reaction to radiation injury and to regional cerebral hemodynamic changes, and we expect similar sequelae to occur in all stereotactic radiosurgery series, regardless of the radiosurgical modality employed. The likelihood of developing symptomatic brain injury from vasogenic edema, vascular occlusion or parenchymal necrosis appears to increase with increasing treatment dose and volume, including the volume of the normal brain traversed in order to reach the target volume [5,7,9]. However, sequelae are not solely dependent on either dose or volume. Many patients have received high doses to very large AVMs without any problem; others have experienced adverse sequelae after receiving low doses to small AVMs [5].

The specific clinical manifestations of brain tissue injury are determined by the region of the brain involved, volume of tissue affected, presence of prior damage from spontaneous hemorrhage or previous surgery, and the timing of therapeutic corticosteroid intervention, if clinically required. Midbrain structures, central nuclei, hypothalamus and corpus callosum appear more sensitive than more peripheral hemispheric structures. However, significant individual biologic variation exists among patients within each category, suggesting that careful selection of treatment dose and volume for various loci within the brain can minimize the risks of stereotactic radiosurgery of the brain, but not eliminate all risks.

References

Sequelae of Stereotactic Radiosurgery


**FIGURE LEGENDS**

**Figure 1:** Cerebral angiograms of a deep right parietal AVM in an 18-y-old female. **Left (upper and lower).** Lateral and anteroposterior views demonstrate
the AVM prior to stereotactic radiosurgery. Middle (Upper and lower). 12 mo after radiosurgery (dose, 20 GyE) there is partial obliteration of the AVM. Right (upper and lower). 24 mo after radiosurgery the AVM is completely obliterated. The patient has remained neurologically normal throughout (cf Figure 2).

**Figure 2**: Sequential T2-weighted MRI scans of the patient shown in Figure 1. Left (upper). Before stereotactic radiosurgery. Right (upper), little change has occurred 8 mo after treatment. Left (lower), vasogenic edema has spread into the the deep white matter of the parietal lobe at 16 mo after treatment; Right (lower), the edema has resolved at 22 mo after treatment. The patient never developed neurologic symptoms and no corticosteroid therapy was required.

**Figure 3**: Sequential MRI scans in a 15-y-old girl with a large (26,000 mm³) left parietal AVM. Left (upper). Before stereotactic radiosurgery. Right (upper), 13 mo after treatment with 32 GyE the initial signs of deep white matter vasogenic edema have appeared; the patient had no symptoms. Left (lower), massive edema has developed 20 mo after treatment, associated with mild hemiparesis; Right (lower), 24 mo after treatment there has been interim resolution of the edema and marked clinical improvement in response to corticosteroid therapy. The edema continued to resolve without further need for steroid therapy, and the patient returned to normal except for a very subtle foot dorsiflexion weakness. The large AVM is fully obliterated.

**Figure 4**: Cerebral angiograms and CT scans of a 15-y-old boy with a residual deep left parietal AVM after partial surgical excision. Upper (left and middle). Lateral and anteroposterior views of the left internal carotid artery injection and (right) contrast-enhanced CT scan demonstrate the AVM prior to radiosurgery. Lower (left, middle and right). Comparable views 12 mo after treatment with 25 GyE demonstrate complete obliteration of the AVM without evidence of edema. This patient developed right-sided hemiparesis that was unresponsive to steroids shortly before the followup studies were performed; small vessel occlusion was responsible for this outcome. He has had an incomplete recovery.

**Figure 5**: Sequential cerebral angiograms and MRI scans of a 40-y-old woman with a very large (40,000 mm³) right temporal AVM. Upper (left), anteroposterior view of the right vertebral artery injection before stereotactic radiosurgery; (middle), axial MRI scan 23 mo after treatment with 28 GyE shows localized white matter edema; (right), complete obliteration of the AVM is seen 27 mo after treatment; the patient was neurologically intact. Lower (left), complete occlusion of the right posterior cerebral artery with associated hemiparesis occurred at 28 mo after treatment; (middle), axial MRI scan at 28 mo after treatment demonstrates regional cerebral infarction. The right posterior cerebral artery was intimately involved in the structure of the AVM and thus in the radiation field. (From M. P. Marks, R. L. DeLaPaz, J. I. Fabrikant, K. A. Frankel, M. H. Phillips, R. P. Levy, and D. R. Enzmann. Imaging of charged-particle stereotactic radio-

**Figure 6:** Cerebral angiograms and MRI scans of a 33-y-old man with a large (18,000 mm³) deep right parietal AVM. **Upper, (left and right),** lateral and anteroposterior views of the right internal carotid artery injection demonstrate the AVM prior to radiosurgery. **Middle, (left and right),** comparable views 12 mo after treatment with 30 GyE demonstrate partial obliteration of the AVM; **Lower, (left and right),** coronal and axial MRI scans 21 mo after treatment show extensive abnormal signal of the right parietal lobe, associated with the development of hemiparesis; cerebral angiography at this time showed complete obliteration of the AVM. The patient’s left-sided weakness improved markedly with corticosteroid therapy, but recurred when steroids were tapered. An exploratory craniotomy 33 mo after treatment revealed radiation necrosis.

**Figure 7:** Cerebral angiograms of a deep right-sided AVM in a 32-y-old male. **Upper (left and right),** lateral and anteroposterior views of the right internal carotid artery injection demonstrate the AVM prior to radiosurgery. A rectangular-shaped “target” (marked in orthogonal projections) was designated for radiosurgical obliteration. **Lower (left and right),** comparable views 34 mo after radiosurgery (dose, 35 GyE). There has been marked obliteration of the abnormal vasculature in the irradiated target, but no change in the unirradiated periphery of the AVM. Radiosurgery treatment plans that fails to encompass the entire arterial phase of the AVM in a uniformly distributed radiation field are no longer consider acceptable.
Table 1. Sequelae in 322 AVM Patients

- Asymptomatic edema - 20%
- Minimal neurologic dysfunction - 4-5%
- Moderate or severe sequelae - 11-12%
  - vasogenic edema - 8%
  - vascular occlusion - 2-3%
  - necrosis - 1%

- Most sequelae are fully or partially reversible.
Figure 6
Figure 7