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Clinical Results of Stereotactic Heavy-Charged-Particle Radiosurgery for Intracranial Angiographically Occult Vascular Malformations

R.P. Levy, J.I. Fabrikant, M.H. Phillips, K.A. Frankel,
G.K. Steinberg, M.P. Marks, R.L. DeLaPaz, F.Y.S. Chuang,
and J.T. Lyman

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DISCLAIMER

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Research Medicine and Radiation Biophysics

Lawrence Berkeley Laboratory

1 Cyclotron Road

Berkeley, CA

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CLINICAL RESULTS OF STEREOTACTIC HEAVY-CHARGED-PARTICLE RADIOSURGERY FOR INTRACRANIAL ANGIOGRAPHICALLY OCCULT VASCULAR MALFORMATIONS [1]

Richard P. Levy[2], Jacob I. Fabrikant[3], Mark H. Phillips[4], Kenneth A. Frankel[5], Gary K. Steinberg[†6], Michael P. Marks[†7], Robert L. DeLaPaz[†8], Frank Y. S. Chuang, and John T. Lyman[9]

Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley, CA and [†]Stanford University Medical Center, Stanford, CA

INTRODUCTION

Angiographically occult vascular malformations (AOVMs) of the brain have been recognized for many years to cause neurologic morbidity and mortality [5]. They generally become symptomatic due to intracranial hemorrhage, focal mass effect, seizures or headaches [5]. Hemorrhage may occur repeatedly, with disabling or fatal consequences [7,10]. The true incidence of AOVMs is unknown, but autopsy studies suggest that they are more common than high-flow angiographically demonstrable arteriovenous malformations (AVMs) [6].

AOVMs have been classified histologically into: (1) thrombosed or slow-flow AVMs; (2) cavernous angiomas; (3) capillary telangiectasias; and (4) venous angiomas [6]. In neurosurgical series, angiographically occult AVMs and cavernous angiomas comprise some 85% of histologically classified AOVMs [5]. Venous angiomas are the most common type of AOVM in consecutive autopsy series, but infrequently are sufficiently symptomatic to come to neurosurgical attention [6].

Complete resection of symptomatic surgically-accessible AOVMs is considered appropriate management, provided the surgical risk is not excessive [5]. However, many deep-seated AOVMs, especially in the deep central nuclei and brain stem, are considered to be inoperable due to their location in or proximity to functionally important brain structures [1].

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[1]Research supported by the Director, Office of Energy, Health and Environmental Research of the United States Department of Energy under Contract DE-AC03-76SF00098.

[2]Medical Scientist, Lawrence Berkeley Laboratory

[3]Professor of Radiology, University of California, San Francisco and Berkeley

[4]Staff Scientist, Lawrence Berkeley Laboratory

[5]Staff Scientist, Lawrence Berkeley Laboratory

[6]Assistant Professor of Neurosurgery, Stanford University

[7]Assistant Professor of Radiology (Neuroradiology), Stanford University

[8]Associate Professor of Radiology (Neuroradiology), Stanford University

[9]Professor of Radiation Oncology, University of California, San Francisco

We have developed stereotactic heavy-charged-particle Bragg peak radiosurgery for the treatment of inoperable intracranial vascular malformations, using the helium ion beams at the Lawrence Berkeley Laboratory 184-inch Synchrocyclotron and Bevatron [2,3,4]. Since 1983, we have treated 31 patients with inoperable AOVMs of the brain. This report describes the protocol for patient selection, radiosurgical treatment planning method, clinical and neuroradiologic results and complications encountered, and discusses the strengths and limitations of the method.

METHOD

Patient selection. The diagnosis of AOVMs and evaluation of prospective patients for stereotactic radiosurgery is based on a multi-institutional clinical research protocol and involves the clinical judgment and neuroradiologic findings of a university panel of neurosurgeons, neuroradiologists and radiotherapists. Diagnostic neuroradiologic criteria include: (1) a cerebral angiogram performed at least 6 to 8 wk after hemorrhage without other evidence of abnormal vascularity; and (2) characteristic magnetic resonance image (MRI) evidence of chronic hemorrhage without edema. MRI scanning was not available in the evaluation of the first few patients; in these individuals, computerized tomography (CT) scanning demonstrating a hyperdense heterogeneous or homogeneous mass with slight contrast enhancement and with appropriate clinical criteria were considered to be diagnostic; these cases were later confirmed by MRI.

Only patients with symptomatic surgically-inaccessible AOVMs and a history of intracranial hemorrhage, progressive nonhemorrhagic neurologic dysfunction and/or refractory seizures are considered to be candidates for the AOVM radiosurgery protocol. Patients with venous angiomas are not included.

Stereotactic neuroradiologic evaluation and treatment planning. Treatment planning for radiosurgery of intracranial angiographically demonstrable AVMs has been described in detail previously [2,3,4]. We have adapted this method to the treatment of AOVMs, by the use of interactive treatment planning with MRI and CT data. Briefly, a removable noninvasive thermoplastic immobilizing mask and nonferromagnetic stereotactic frame have been developed for correlation and data transfer between sequential stereotactic MRI and CT scans for treatment planning and subsequent radiosurgery [8]. The composite information from the MRI and CT scans is used to delineate stereotactically the target volume for radiosurgery for conformal treatment planning. Three-dimensional treatment plans are developed and evaluated to provide optimal dose distribution in the target volume, with satisfactory dose sparing and protection of adjacent critical brain structures. Computer-assisted image correlation between multiplanar MRI and CT scans provides explicit demonstration of selected isodose contour distributions in the brain in all desired anatomic planes (Figure 1) [8].

The helium-ion beam is shaped by individually designed apertures and compensators to conform to the size, shape and location of the AOVM. The target volume is defined by the entire region of abnormality demonstrated by MRI and CT scanning. The range and width of the Bragg ionization peak are determined by appropriate absorbers in the beam path, thereby creating a three-dimensional high-dose volume of desired shape placed stereotactically within the brain. Multiple entry angles and beam ports are selected so that the high-dose Bragg peak regions of the individual beams converge within the lesion (Figure 1) [4]. Patient immobilization and precision dose localization are effected by the stereotactic patient positioning apparatus (ISAH), which is an integral component of the beam delivery system within the treatment room [4]. All patients are treated on an ambulatory basis.

Treatment dose and fractionation. Initially, maximal central doses of 45 GyE[10] (34.5 Gy) were used for treatment of AOVMs, based on the protocol and experience for treatment of angiographically demonstrable AVMs. As part of a dose de-escalation trial, subsequent patients with AOVMs were treated at progressively lower doses usually with four coplanar or noncoplanar beams; currently, doses of 15, 20 and 25 GyE are used, depending on a number of factors. Two patients who had received prior conventional radiation therapy and one patient with a large hypothalamic lesion were treated with 10 GyE. Most patients were treated with 1 fraction. All patients are started on a course of low-dose dexamethasone 1 day prior to treatment, and which is gradually withdrawn.

Patient followup. Patients treated for AOVMs are examined on a regular basis, defined by the protocol, by us and by their referring physicians. MRI scanning is performed at 6-mon intervals to assess the response to treatment and to identify early or late delayed radiation injury or edema in the brain, should they occur, and to guide appropriate manangement.

RESULTS

Patient selection. We have thus far treated 31 patients with intracranial AOVMs in the clinical research protocol; all AOVMs were deep and considered to be surgically-inaccessible. There were 18 males and 13 females; ages from 13 to 64 y. Seventeen AOVMs were in the brain stem, 8 in the thalamus or internal capsule, 3 in the deep cerebral hemisphere or motor cortex, 2 in the basal ganglia, and 1 in the cerebellopontine angle. Treatment volumes ranged from 80 to 10,200 mm^3.

Eleven patients were neurologically normal, 18 had mild to moderate stable neurologic deficit, and 2 had actively progressing neurologic dysfunction at the time they were entered into the protocol. There was clinical and radiologic evidence of

[10]1 Gy = 1 gray = 100 rads; Gy equivalent (GyE) = the product of the appropriate relative biologic effectiveness (RBE) x the physical dose in Gy delivered by the charged-particle beam. We have determined that the RBE for the helium ion beam Bragg peak is approximately 1.3.

hemorrhage in all patients; most had hemorrhaged repeatedly. Six patients manifested varying degrees of chronic headache; 5 had hydrocephalus; 12 had some neurologic dysfunction not immediately related to hemorrhage; and 2 had seizure disorders. Several patients had various combinations of multiple signs and symptoms.

Most patients had received no interventional therapy prior to stereotactic radiosurgery. Four patients had prior placement of ventriculo-peritoneal shunts; 4 had hematoma evacuation or exploration and/or partial excision of the AOVM; and 1 had surgical excision of a separate surgically-accessible vascular lesion. Two patients referred to the protocol had previously received large-field conventional multifractionated radiotherapy (approximately 50 Gy) and chemotherapy at other institutions for presumed brain stem glioma.

Clinical followup. All patients completed the course of stereotactic neuroradiologic evaluation and radiosurgical treatment without difficulty; none required sedation or anesthesia. Of the 31 patients, 22 have been followed for at least 2 y; 29 have been followed for more than 1 y. The majority of patients have had favorable outcomes after radiosurgery. All 11 patients who were neurologically intact at the time of treatment have remained normal. Of the 18 patients who had a relatively stable neurologic deficit at the time of treatment, 6 have improved (2 are now normal), 7 have remained unchanged, and 5 have worsened. Two patients who had previously undergone therapy for presumed brain tumor were admitted to the radiosurgery protocol at the time they had rapidly progressive deterioration; both continued to have a downhill course and died from pneumonia at 9 and 14 mon after treatment, respectively. Six patients had recurrent hemorrhage after treatment; 5 within 13 mon and 1 at 19 mon following radiosurgery. Three of the 6 recovered to their previous neurologic status; the other 3 worsened.

Neuroradiologic followup. After radiosurgery, several patients, including 1 with concomitant clinical worsening, have developed vasogenic edema on T2-weighted MRI scans. Most patients demonstrated little change on MRI scans over time, other than what could be explained by partial resorption or evolution of pre-existing hemorrhage. No AOVM underwent radiologic changes that could be interpreted as demonstrating complete luminal obliteration of abnormal vascular structures comparable to that seen with high-flow angiographically demonstrable AVMs [4].

Sequelae. Four patients had possible or probable adverse sequelae of radiosurgery, as direct or indirect brain tissue reaction to injury. One patient with an AOVM of the right internal capsule and thalamus developed transient reversible mild hemiparesis 9 mon after treatment with 35 GyE to a volume of 850 mm^3, due to localized radiation-induced edema or small vessel injury; the neurologic dysfunction did not respond initially to corticosteroids, but the patient's deficit resolved completely over several months without further use of steroids. One patient with a pontine AOVM who initially presented with ataxia developed worsening dysequilibrium and cranial

nerve dysfunction 5 mon after treatment with 20 GyE to a volume of 1,200 mm^3 possibly due to recurrent small hemorrhage or mass effect unrelated to radiosurgery, based on MRI and CT examinations. One patient with a midbrain AOVM developed worsening diplopia and ataxia 3 to 4 mon after treatment with 20 GyE to a volume of 1,000 mm^3, associated with MRI evidence of radiation-induced edema; these symptoms partially resolved with corticosteroid therapy. One patient with a very large, 10,200 mm^3 hypothalamic AOVM experienced several episodes of marked deterioration and complete recovery about 1 y after treatment with 10 GyE; no evidence of radiation injury was seen on MRI or CT scans, but small vessel injury may have occurred.

DISCUSSION

Patient selection. The 31 patients with AOVMs in this series generally became symptomatic due to intracranial hemorrhage or local mass effect. Progressive neurologic deterioration was typically characterized by intermittent episodes of worsening and stabilization [5]. Although CT scanning has been shown to be a sensitive means for detecting AOVMs, radiologic differentiation of AOVMs from partially calcified, avascular low-grade gliomas was difficult [5]. In some cases the MRI appearance of these AOVMs could be suggestive of hemorrhagic neoplasms, especially if a relatively recent hemorrhage had occurred, but the pattern of evolution of the hematoma on serial MRI scans in our patients generally permitted this distinction. For example, neoplasms frequently manifest edema and evidence of nonhemorrhagic tumor tissue, and rarely produce the circumferential hemosiderin deposition typically demonstrated in the parenchyma adjacent to AOVMs [9].

Although the diagnosis of AOVMs has become more accurate, neither the clinical history nor the radiologic appearance was pathognomonic for this entity. Ogilvy et al [7] have reported that some patients with a history of recurrent hemorrhage over a period of many years, with CT and MRI scans characteristic of AOVMs, have been found at surgery to have low-grade astrocytomas. Conversely, some patients who had previously been diagnosed and treated for presumed glioma recently have been diagnosed with AOVMs by characteristic MRI findings; 2 cases are included in our series, 1 with capillary telangiectasia confirmed at autopsy.

The anatomic distribution of the AOVMs in our series reflects the protocol selection bias for surgically-inaccessible lesions. Of 31 cases 55% were in the brain stem and 32% in the deep central nuclei or internal capsule. Lobato et al [5] have reported that brain stem (11%) and "deep location" (22%) AOVMs constitute a minority of operated cases. This difference in anatomic distribution should be considered when comparing clinical and neuroradiologic results in this radiosurgical series of extremely high-risk patients with most reported neurosurgical series [1].

Heavy-charged-particle radiosurgery. The physical characteristics of heavy-charged-particle beams are highly advantageous for the radiosurgical treatment of discrete

intracranial target volumes [2,3,4]; these beams are uniquely adaptable to the treatment of deep-seated and centrally located targets while protecting, to the extent possible, adjacent central brain structures. Bragg peak radiosurgery can be used with precision to treat irregular lesions of very large size, as well as to deliver extremely sharp focal beams accurately to small centrally located AOVMs [2,3,4].

The appropriate choice of the radiosurgical target volume in the treatment of AOVMs is important. Accurate localization of the abnormal vasculature is fairly straightforward with most angiographically demonstrable AVMs, but not with AOVMs. Neuroradiologic methods generally do not demonstrate the AOVM itself, but rather the characteristic sequelae of acute and/or chronic hemorrhage into the adjacent brain parenchyma [9]. AOVMs frequently hemorrhage eccentrically and are found during surgery only by a careful exploration of the wall of the hematoma cavity [10]. Therefore, the target volume for the radiosurgical treatment of AOVMs would appear to be the entire region of abnormality defined by MRI scanning. However, this treatment strategy may result in the irradiation of some healthy brain tissue in eloquent locations at the periphery of the hematoma. We believe that the best approach is to treat the entire volume defined by the abnormal MRI signal, but to use a conservative dose for centrally located AOVMs. Currently, we treat to maximum doses of 15 GyE in most cases, with the 90% isodose contour at the periphery of the target volume. Doses of 10 GyE are used only in selected cases, e.g., unusually large AOVMs.

Patient followup. MRI scanning is useful in following patients after stereotactic radiosurgery for evidence of delayed edema or parenchymal radiation injury. Delayed radiation injury may be manifested by asymptomatic or symptomatic vasogenic edema, occlusion of small functional blood vessels, or radiation necrosis. Often it is not possible to determine whether a worsening clinical status in a patient resulted from radiation injury or from a hemorrhagic event or mass effect too small to be resolved by MRI scanning, but unrelated to radiosurgery. Many conservatively-managed patients with AOVMs exhibit an episodic clinical course, without apparent interval change in their CT and/or MRI scans [4,5]; this was the case in 3 of the 4 patients reported in this series to have experienced possible or probable complications.

We consider the clinical results in this series of 31 patients with deep, surgically-inaccessible AOVMs treated with stereotactic heavy-charged-particle Bragg peak radiosurgery to be promising. Most patients in this high-risk group have done well clinically and while all patients presented with a history of intracranial hemorrhage, thus far only 1 patient hemorrhaged after 13 mon following radiosurgery. All patients who were normal at the time of radiosurgery have remained normal; most patients who had some neurologic deficit at the time of treatment have improved or their condition has stabilized. Complications encountered in this series of patients thus far have been relatively uncommon. However, even a limited degree of

parenchymal radiation injury can lead to major neurologic sequelae if it occurs in deep central brain structures.

CONCLUSIONS

Considerable clinical research is required to define more precisely the selection criteria for stereotactic radiosurgery in patients with AOVMs. The optimal treatment dose and radiosurgical target volume must be determined for the treatment of AOVMs in various locations within the brain. Neuroradiologic imaging methods are presently not able to demonstrate the vascular structures in most AOVMs or obliterative changes in response to stereotactic radiosurgery, unlike the situation with angiographically demonstrable AVMs. The absence of such a neuroradiologic standard for assessing the successful response of AOVMs to radiosurgery makes it imperative that long-term clinical follow-up be continued.

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FIGURE LEGEND

Figure 1: Stereotactic heavy-charged-particle Bragg peak radiosurgery treatment planning for an angiographically occult vascular malformation of the pons. **Left, upper and lower.** Stereotactic MRI scans in the axial and sagittal planes are used to define the target volume (ring of white dots) for stereotactic radiosurgery. The target contour data are transferred to corresponding images on the stereotactic CT scans, using a VAX 11/780 computer system. **Middle, upper and lower**. CT data are then used to identify and compensate for inhomogeneities in the tissues to be traversed by the charged-particle beams and to calculate three-dimensional dose distribution contours. The dose contour information is then transferred back to the original MRI scans **(right, upper and lower)** to permit the explicit demonstration (and modification, where required) of isodose contour distributions in the brain in all desired anatomic planes. Isodose contours displayed here in the axial and sagittal planes are calculated for 10, 50, 70, and 90% of the maximum dose [8].

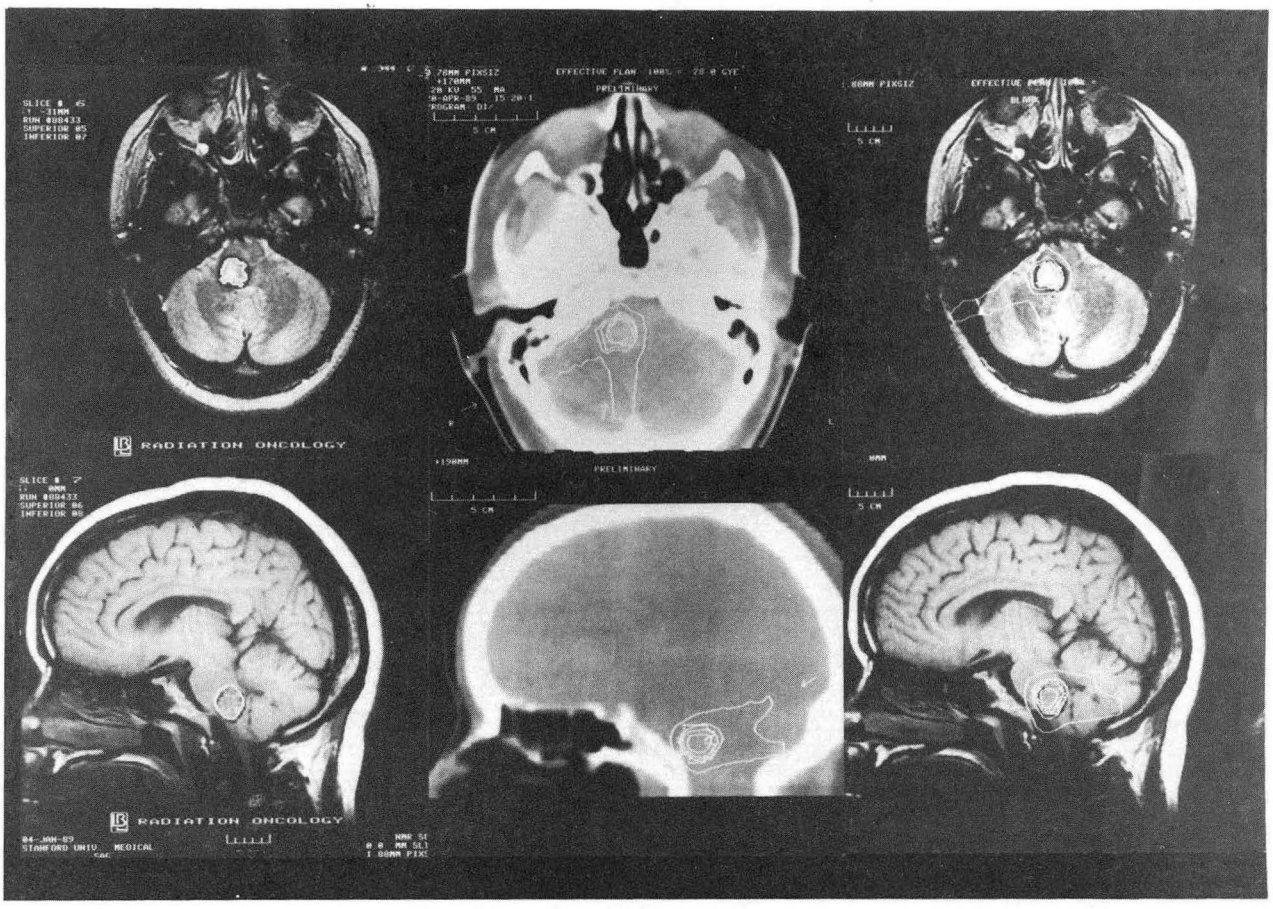

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Figure 1

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