Title
STEREOTATIC HEAVY-CHARGED-PARTICLE BRAGG PEAK RADIOSURGERY FOR THE TREATMENT OF INTRACRANIAL ARTERIOVENOUS MALFORMATIONS IN CHILDHOOD AND ADOLESCENCE

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STEREOTACTIC HEAVY-CHARGED-PARTICLE
BRAGG PEAK RADIOSURGERY
FOR THE TREATMENT OF
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IN CHILDHOOD AND ADOLESCENCE

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ABSTRACT

Forty patients aged 6 to 18 y have now been treated for inoperable intracranial arteriovenous malformations (AVMs) using stereotactic heavy-charged-particle Bragg peak radiosurgery at the Lawrence Berkeley Laboratory 184-inch Synchrocyclotron at the University of California Berkeley. This paper describes the procedures for selection of patients, the treatment protocol, and the neurologic and neuroradiologic responses to stereotactic radiosurgery in this age group. The AVM volumes treated ranged from 265 mm$^3$ to 60,000 mm$^3$. The results are favorable; 20 of 25 patients have thus far had $\geq 50\%$ obliteration of the AVM within 1 y after treatment and 14 of 18 patients have thus far had total obliteration of the AVM by 2 y after treatment. Two patients hemorrhaged from a radiosurgically-treated AVM within 12 mo following treatment, but none thereafter. Complications include vaso­genic edema and arterial occlusion; three patients have had neurologic worsening as definite or possible sequelae of treatment. The strengths and limitations of the method are discussed.

Key Words: arteriovenous malformation, Bragg peak radiosurgery, heavy-charged-particles, intracranial hemorrhage, pediatric neurology, radiosurgery, stereotactic radiosurgery
INTRODUCTION

One of the more challenging problems of vascular neurosurgery in childhood and adolescence is the management of surgically-inaccessible deep-seated arteriovenous malformations (AVMs) of the brain [17,26]. Conventional multifractionated x-ray therapy of AVMs has been generally unsuccessful [12]. Steiner et al [34,35,36] have used stereotactic irradiation with narrow beams delivered in a single dose from a multisource cobalt-60 gamma unit to achieve obliteration of small AVMs (less than 4,000 mm³). Kjellberg et al [13,14,16] have applied stereotactic radiosurgery to the treatment of intracranial AVMs using the Bragg ionization peak of a proton beam. Podgorsak, Sturm, Winston and their colleagues [29,37,41] and others have recently initiated stereotactic radiosurgery procedures using modified linear accelerator methods.

At Lawrence Berkeley Laboratory at the University of California Berkeley, in collaboration with the University of California San Francisco Medical Center and Stanford University Medical Center, we have developed the method of stereotactic heavy-charged-particle Bragg peak radiosurgery for treatment of inoperable intracranial AVMs, using the helium ion beam delivered at the 184-inch Synchrocyclotron [7,8,9,21,23,24,33]. We have treated 40 patients aged 6 to 18 y since 1982. This report describes patient selection, treatment method, clinical and neuroradiologic results and complications encountered, and discusses the strengths and limitations of the method in this age group.

METHOD

PATIENT SELECTION. All prospective patients are evaluated by our stereotactic radiosurgery team of radiologists, physicians and physicists together with neurosurgeons and neuroradiologists at the collaborating university hospitals. Patients are considered to be candidates for the multi-institutional clinical protocol if they have a history of intracranial hemorrhage, nonhemorrhagic neurologic dysfunction, intractable vascular headaches or refractory seizures. Radiosurgery is performed only on symptomatic patients with AVMs that are considered surgically-inaccessible by our collaborating neurosurgeons. After the diagnosis of AVM is confirmed and it is agreed that radiosurgical treatment is indicated, recommendations are made on a case-by-case basis concerning the appropriate role of embolization prior to radiosurgery. Embolization is carried out in order to reduce the size of the AVM and/or the rate of blood flow through the AVM in preparation for radiosurgery. Some
patients have had surgical ligation of feeding vessels or partial operative resection of the AVM or embolization prior to referral for stereotactic radiosurgery. More frequently, neither surgery nor embolization is feasible, particularly for deep AVMs located in the brainstem and adjacent nuclei. Some patients have had a limited surgical procedure previously, such as shunt placement or hematoma evacuation, but without AVM vessel ligation or resection. The cerebral angiograms of all patients are examined for concomitant arterial aneurysms. Aneurysms are treated only by surgical or interventional neuroradiologic procedures [35].

Angiographically-occult (cryptic) AVMs are diagnosed by a normal cerebral angiogram and characteristic magnetic resonance image (MRI) findings of heterogeneous signal indicating a region of chronic hemorrhage without edema or evidence of systemic or focal neoplasia [25,38]. Parental (or subject) informed consent is obtained for each patient. Institutional authorization for conduct of human clinical research and treatment has been obtained from Lawrence Berkeley Laboratory and all cooperating university centers collaborating in this study.

**STEREOTACTIC NEURORADIOLOGIC EVALUATION.** This radiosurgical method has been described in detail in previous publications [7,8,9,21,23,24]. A removable noninvasive thermoplastic immobilizing mask and stereotactic frame, modified from the concept of the Leksell frame, have been developed for stereotactic localization of the AVM and subsequent radiosurgery [9,18,24]. The mask and frame system permits reliable correlation and data transfer between sequential stereotactic cerebral angiography and stereotactic multiplanar x-ray computerized tomography (CT) and MRI scans [24,27]. These studies may be performed in any order, generally over a 1 to 2 day period. Stereotactic cerebral angiography is not performed on patients with known angiographically-cryptic AVMs; here, stereotactic MRI scanning is used to identify the size, shape and location of the lesion.

**STEREOTACTIC RADIOSURGICAL TREATMENT PLANNING.** The composite three dimensional contour information derived from the neuroradiologic studies is used to delineate stereotactically the appropriate tissue target, and to calculate the AVM volume. The helium ion beam (230 MeV/amu\(^1\)) at the 184-inch Synchrocyclotron is shaped by individually-fabricated brass and cerrobend apertures to conform precisely to the contours of the AVM and to any cross-section width from 4 to 80 mm. The range (i.e., the distance that a particle of a given energy travels in tissue) of the Bragg ionization peak in the direction of the beam is determined by interposing a tissue-equivalent absorber in the beam.

\(^1\)MeV/amu=million electron volts per atomic mass unit
Heavy Particle AVM Radiosurgery / RP Levy

path; this range is further modified by use of individually-designed lucite compensators. The width of the spread Bragg peak in the direction of the beam path is determined by interposing a rotating filter; this permits prescribed spreading of the peak up to 50 mm or more [6,8,9,19,21,22,23]. Thus, each beam is uniquely tailored to place a three-dimensional high dose region of desired shape stereotactically within the brain (Fig. 1).

Multiple entry angles and beam ports are chosen so that the high-dose Bragg peak regions of the individual beams intersect within the AVM target. CT scan data are used to identify and compensate for inhomogeneities in the tissues traversed by the charged-particle beams and to calculate the dose distribution in each patient, using a VAX 11/780 computer system [2,40]. Composite isodose-distribution curves are plotted on reconstructed stereotactic CT and/or MR images (Figs. 2,3B,4B) and optimal heavy-charged-particle treatment plans are selected for treatment of the target volume and protection of critical brain structures in each patient [8,9,21,23]. Stereotactically-directed focal charged-particle beams are used to irradiate the main arterial feeders and shunting vessels of the malformation, and to include, as completely as possible, the whole cluster of pathologic arterial shunting vasculature within a uniform radiation field (Figs. 2,3B,4B). Reliable immobilization of the patient and beam localization have been achieved in our isocentric stereotactic patient positioner [20,24]. All patients are treated on an ambulatory basis.

**Radiosurgical Treatment Dose and Fractionation.** Initially, maximum central (100%) doses of 45 GyE \(^2\) (34.5 Gy) were used, with larger AVMs or those in more sensitive regions receiving 35 to 40 GyE (26.9 to 30.8 Gy). Successful obliteration of AVMs at the lower end of this range led us to scale down doses in a stepwise fashion, to determine the lowest effective dose. Thus, subsequent patients were treated with 25 to 35 GyE (19.2 to 26.9 Gy). Currently, maximum central doses of 15 to 25 GyE (11.5 to 19.2 Gy) are used. Smaller or supratentorial AVMs are treated with higher doses than larger or brainstem lesions. Densely packed AVMs are treated to higher doses than those loosely intertwined with normal brain tissue. The periphery of the target is enclosed by the 90% isodose contour (Figs. 2,3B,4B). The dose to the normal brain adjacent to the AVM is considerably less than the dose to the AVM target volume. Dose fall-off to less than 10% of the maximum dose occurs within 4 to 6 mm of the target distally, and within 2 to 3 mm.
along the lateral margins of the helium-ion beam (Fig. 2).

As many as 3 fractions were used initially, based on previous experience in this laboratory with helium beam irradiation of the pituitary. Currently, treatment is given in 1 or 2 daily fractions, 3 to 5 ports per fraction. Each fraction requires less than 1 h of patient immobilization, mostly to verify positioning, and each port requires about 1 min of irradiation. Lesions less than 4,000 mm$^3$ are generally treated in 1 d; larger lesions are generally treated in 2 d.

Specific dose and fraction selection depends on the size and location of the AVM within the brain, and the volume of normal brain tissue through which the beams must pass. All patients are placed on low-dose dexamethasone 1 d prior to treatment and this is gradually withdrawn over a 2 wk period.

PATIENT FOLLOW-UP. Patients are examined on a regular follow-up basis by us and/or their referring neurosurgeons or neurologists. Our protocol requires that follow-up cerebral angiography be performed at 12-mo intervals until the AVM has been completely obliterated, or has stabilized with no further decrease in size; this requires regular angiographic follow-up for as long as 2-4 y. In younger children, when general anesthesia is required for cerebral angiography, we have had the first follow-up angiographic studies after 2 y. Unless contraindicated, patients are also studied by MRI scans 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. Additionally, CT scans are performed every 12 mo and correlated with MRI scans and cerebral angiograms. Patients with angiographically-occult AVMs are followed by MRI scanning at 6-mo intervals and CT scanning yearly; follow-up angiography is not performed.

RESULTS

PATIENTS. We have thus far evaluated and treated 40 patients ranging in age from 6 to 18 y, median 14 y (Tables 1 and 2). There are 25 males and 15 females. Sixteen patients had AVMs in the cerebral hemispheres, primarily involving eloquent regions of motor or speech function. There were 18 patients with AVMs located in the basal ganglia or thalamus. The remaining 6 malformations were in the hypothalamus, pons, or other brainstem structures, and vein of Galen aneurysms. There were 3 angiographically-cryptic AVMs (Table 2). The calculated AVM volumes ranged from 265 mm$^3$ to 60,000 mm$^3$ (median, 7,050 mm$^3$); 18 were under 4,000 mm$^3$. 
Table 3 lists the clinical manifestations of the 40 patients prior to radiosurgery. All patients were symptomatic. The most common presentation was intracranial hemorrhage; this occurred in 24 patients. Other clinical manifestations (Table 3) were included only when these were not directly associated with acute intracranial hemorrhage, i.e., seizures, headaches, nonhemorrhagic progressive or fixed neurologic deficits, or presence of or hemorrhage from associated arterial aneurysms. Many patients had some combination of these. The category of nonhemorrhagic neurologic symptoms or deficits includes fixed or transient focal weakness or sensory dysfunction, and learning or behavioral disabilities, when these could be attributed to the AVM, e.g., when associated with a vascular steal.

Seventeen patients had no interventional therapy prior to stereotactic radiosurgery. Eight patients had one or more adjunct procedures (e.g., shunt placement, arterial aneurysm repair, hematoma evacuation) that were not intended to result in any decrease in AVM size or blood flow. Fifteen patients had some form of AVM surgery and/or AVM embolization before radiosurgery; thus, radiosurgery was the only method used to treat the AVM in 25 patients. Various combinations of multiple preradiosurgery therapeutic interventions were carried out in 7 patients (Table 4).

Six patients were found to have arterial aneurysms that were detected on cerebral angiography at the time of their initial evaluation for stereotactic radiosurgery. One additional patient had an aneurysm discovered by cerebral angiography 2 y after radiosurgery, at the time the AVM had been mostly obliterated; the aneurysm had previously been concealed within the dense cluster of the AVM vessels. Often it is not possible to distinguish whether a hemorrhage originates from an associated aneurysm or from the AVM.

All patients completed the course of stereotactic neuroradiologic evaluation and treatment without difficulty; all tolerated the procedures well and were very cooperative. None required sedation or anesthesia during the radiosurgical treatment, although smaller children did receive general anesthesia during their diagnostic stereotactic cerebral angiograms.

**NEUROLOGIC AND NEURORADIOLOGIC FOLLOW-UP.** Twenty-six patients of the 40 have remained normal or have improved clinically to normal neurologic status following stereotactic radiosurgery. One patient has improved significantly, but still has a mild neurologic deficit. Nine patients have fixed neurologic deficits, unchanged from before treatment; 3 have worsened. One patient has been lost to follow-up (Tables 1 and 2).

The effects of radiosurgery on seizure or headache frequency or intensity are difficult to quantify, due to their often intermittent and/or subjective nature. Multiple associated vari-
ables (e.g., medication compliance, psychological factors) complicate analysis. A 15-y-old girl (patient No. 8) who presented with frequent difficult-to-control seizures has obtained excellent seizure control since radiosurgery successfully obliterated her AVM; a similar response was reported for patient No. 19. Two patients presenting with chronic headaches (Nos. 5, 17) reported marked improvement associated with partial or complete radiosurgical obliteration of their AVMs. None of the 40 patients have had worsening of control of seizures or headaches.

Table 5 summarizes neuroradiologic follow-up evaluation by cerebral angiography and/or MRI scanning, and also tabulates the response when only cerebral angiographic studies are considered; cryptic AVMs are not included. Of 25 patients studied (19 by cerebral angiography) at 1 y after stereotactic radiosurgery, 10 had complete and 3 had near-complete (≥95%) obliteration of their AVMs, and 7 had substantial partial (≥50%) obliteration. Five patients had minimal (<50%) or no radiologic change.

When neuroradiologic follow-up was extended to 2 y in 18 patients (13 by cerebral angiography), 14 patients had complete obliteration of their AVMs; this includes 2 patients who had had incomplete response at 1 y (Table 5). Two patients had ≥50% partial response at 2 y and 2 patients showed minimal (<50%) change or no evidence of obliteration on cerebral angiography.

Figure 3A illustrates the pretreatment (upper) and 1 y follow-up (lower) cerebral angiograms of a 10-year-old boy (patient No. 12) who had hemorrhaged from a large (26,000 mm³) right frontal AVM. Extreme vascular friability and hemorrhage limited an attempted surgical resection to hematoma evacuation and biopsy. Figure 3B shows the treatment isodose contours plotted on a central CT scan. The 90% isodose contour conforms to and circumscribes the AVM volume and the 10% isodose contour completely spares the contralateral hemisphere. At 1 y following radiosurgery, the cerebral angiogram (Fig. 3A, lower) demonstrated complete obliteration of the AVM.

We have found that MRI scanning correlates very well with cerebral angiography in assessing the response of an AVM to radiosurgery and has proven to be an accurate non-invasive method for serial imaging of radiosurgically-treated AVMs [25]. Conversely, CT scanning has proven to be of very limited value in following vascular changes. Figure 4A illustrates representative pretreatment and 16-mo follow-up MRI scans of a 6-y-old girl (patient No. 21) with a large left thalamic AVM. The follow-up scan demonstrates that the AVM has been almost completely obliterated and that the thalamus has been preserved.
We are examining this child with MRI scanning every 6 mo until complete obliteration of the AVM has been attained or stabilization has resulted on the MRI scan. At that time cerebral angiography will be performed to confirm the MRI findings. Figure 4B shows the treatment isodose contours plotted on a central CT scan. The 90% contour conforms to and circumscribes the AVM volume and the 10% isodose contour completely spares the contralateral hemisphere.

We have seen angiographic changes of vascular obliteration continue beyond 24 mo in a few cases, but stabilization generally occurs at about 18-24 mo after treatment. One 7- y-old boy (patient No. 6) who had initially presented with intracranial hemorrhage from a vein of Galen malformation had no significant vascular response at 2 y after irradiation but he remained asymptomatic. Ultimately his malformation was fully obliterated electively by multiple microcatheter-directed embolizations (using a new generation of equipment that had not been previously available), combined with surgery. He remains neurologically intact 4.5 y after radiosurgery. In one other case, heavy-charged-particle radiosurgery has converted a previously surgically-inaccessible AVM to a smaller size amenable to surgical excision of the residual AVM.

Four of the 5 patients whose vascular malformations have thus far had less than 50% obliteration fall into two special treatment categories. Two patients had vein of Galen malformations with a venous varix. Two other patients had radiosurgical treatment limited (on recommendation of the protocol neurosurgeon) to that small portion of the AVM considered to be the earliest filling arterial vessels rather than to the entire arterial phase of the AVM; both of these patients have had obliteration of the abnormal vasculature in the irradiated target volume, but no change in the unirradiated periphery of the AVM. Similarly, one girl (patient No. 10) who had an 80% response at 2 y had complete obliteration of the treated portion of her AVM, but the untreated portion remained unchanged.

Three patients had angiographically-occult AVMs and follow-up cerebral angiography will not been performed. These patients are followed with MRI scanning. One patient with a pontine AVM has worsened clinically, but his MRI scan has not changed. A second patient has been stable and early MRI scanning at 7 mo follow-up has shown no change in the AVM. A third patient has not as yet had his first follow-up MRI study. The temporal pattern and interpretation of MRI findings of cryptic AVMs following radiosurgery is the subject of continuing investigation in our laboratory.

*INTRACRANIAL HEMORRHAGE AFTER TREATMENT.* Four patients had intracra-
nial hemorrhage following radiosurgery, but only 2 bled from a radiosurgically-treated AVM. One patient hemorrhaged 39 mo after treatment, even though the irradiated AVM had been obliterated 12 mo previously, as demonstrated on angiographic examination. In this unusual case, four discrete AVMs could be demonstrated in the cerebral vasculature after this hemorrhage that had not been present on prior cerebral angiography. The patient bled from a location remote from the the previously irradiated AVM and well outside the treatment fields; this was confirmed by correlation of neuroradiologic examinations with isodose contours and treatment plans. This hemorrhage resulted in worsening neurologic function. Another patient hemorrhaged 16 mo after treatment from a previously unrecognized arterial aneurysm that had been imbedded within the AVM cluster of vessels prior to treatment; this patient had a rapid recovery to his previous level of neurologic function. The aneurysm was subsequently occluded by balloon embolization. A third patient sustained a small hemorrhage 6 mo after treatment; she quickly returned to normal and follow-up study at 12 mo demonstrated complete obliteration of the AVM. A fourth patient, whose AVM irradiation was confined to the early arterial phase feeding vessel cluster, sustained a small hemorrhage 12 mo after radiosurgery, but recovered fully within a few days; MRI scans demonstrated residual AVM in the unirradiated periphery and angiographic follow-up has been deferred for another year. Therefore, 2 patients out of the 40 in our series sustained an intracranial hemorrhage from a radiosurgically-treated AVM, and none after 12 mo following treatment.

**COMPLICATIONS.** Three patients experienced neurologic worsening as definite or possible sequelae of radiosurgery. A 15-y-old girl (patient No. 11) who had presented with seizures from a large (26,000 mm³) left parietal AVM developed mild right hemiparesis from progressive vasogenic edema in the irradiated region, as demonstrated by MRI scanning (Fig. 5). At 13 mo after treatment she was neurologically asymptomatic despite the appearance of edema at the treatment site; at 20 mo she developed increasing edema and mild right-sided weakness, but responded promptly to corticosteroid therapy; clinical improvement continued at 24 mo and the edema began to subside even as steroid therapy was tapered; by 30 mo the edema had diminished further and steroid therapy was discontinued. Currently, 34 mo after radiosurgery, the edema has continued to regress. Subtle dorsiflexion weakness of the right foot, manifested only during competitive running, is the only evidence of very minimal neurologic dysfunction; this has continued to improve steadily. The large AVM has been fully obliterated.

A 15-y-old boy (patient No. 25) who had initially presented with hemorrhage from a
deep left parietal AVM experienced progressive right-sided weakness 8 mo after treatment, unresponsive to corticosteroids; this improved markedly during the subsequent 6 mo, but moderate distal arm weakness and spasticity persist. This probably developed as a consequence of occlusion of some small normal arterial vessels within or immediately adjacent to the malformation. Cerebral angiography has confirmed that the AVM has been fully obliterated; no vascular pathology can be demonstrated.

A 14-y-old boy (patient No. 38) with a cryptic pontine AVM who had presented initially with hemorrhage, cranial nerve dysfunction and ataxia suddenly developed worsening ataxia and cranial nerve palsies of unknown etiology 4 mo after treatment, unresponsive to corticosteroids. This may have resulted from recurrent small hemorrhage or mass effect from the AVM unrelated to radiosurgery. However, radiation-associated thrombosis of vessels intertwined within the AVM and resultant focal infarction and/or mild edema could not be excluded with certainty on the MRI and CT examinations.

No other complications of radiation-associated injury leading to neurologic deficit have been observed in the remaining 37 patients. However, long-term follow-up of 8 of the 40 patients has not yet reached beyond 1 y.

**DISCUSSION**

Improvements in CT scanning and recent developments in MRI scanning have led to the identification of many intracranial AVMs at mildly symptomatic and at asymptomatic stages. With the introduction of stereotactic radiosurgery, interventional neuroradiologic procedures and advances in microscopic neurovascular surgery, the management of intracranial AVMs now requires evaluation of integrated multistage treatment procedures on a case-by-case basis [10]. Complete surgical resection of intracranial AVMs that have hemorrhaged previously is considered to be the appropriate management, provided the surgical risk is not excessive [4,5]; the indications for therapeutic intervention are not well established when AVMs are asymptomatic or become manifest in ways other than hemorrhage [3,10]. Embolization may be helpful in reducing the size and blood flow of some high-flow AVMs, but rarely produces complete obliteration of large or deep malformations [32]. Large AVMs or those involving speech or motor function, the thalamus, basal ganglia, internal and external capsule, and brainstem present extraordinary surgical problems and are frequently associated with high risk [39]. In recent years stereotactic radiosurgery has proven to be a valuable alternative for treatment of this surgically-inaccessible group [7,8,14,18,35].
The physical characteristics of heavy-charged-particle beams are considered to be uniquely advantageous for the radiosurgical treatment of discrete and defined intracranial target volumes [30]. Studies in this laboratory have demonstrated that the radiation dose with this method to normal brain structures adjacent to and remote from the AVM is relatively low, particularly when compared to photon irradiation techniques; this difference appears especially marked in the treatment of larger AVMs [28]. Bragg peak radiosurgery can be used with precision to treat eccentric and irregular AVMs of very large size, as well as to deliver extremely sharp focal beams accurately to small central lesions, including brainstem AVMs (Fig. 2). In this series of 40 young patients, we have treated AVM volumes ranging from only 265 mm$^3$ (8 mm diameter) to 60,000 mm$^3$ (6 cm diameter); we have treated even larger volumes in older patients.

It appears that the entire arterial phase of the AVM cluster must be irradiated uniformly to obtain an optimal result from stereotactic radiosurgery. Attempts to achieve complete AVM obliteration by identifying and treating only the earliest arterial feeding vessels of the AVM, sometimes referred to as the nidus, rather than the entire arterial phase, have resulted in an incomplete response in several of our pediatric patients; undesirable pathologic shunts remain. We have observed this same response in our adult patient population.

The suboptimal response of vein of Galen malformations may reflect the difficulty of identifying and targeting for obliteration all arterial shunting vessels in this type of lesion, compared to other more readily delineated malformations. Differences in the radiation sensitivity of this malformation, possibly due to the histologic structure, may play some role, as well [11].

Stereotactic heavy-charged-particle radiosurgery offers the possibility of complete obliteration of inoperable AVMs and permanent protection against intracranial hemorrhage. It has been suggested that there may be a decrease in the overall frequency of intracranial bleeding as a result of thickening of the walls of the residual shunting vessels or feeders even when only part of the cluster of pathologic vessels is obliterated, although this remains unproven [15]. Preliminary observations in our series of more than 300 patients of all ages suggest that this protection may begin to occur after 6 to 12 mo, even when there have been no grossly discernible vascular changes on cerebral angiography.

Delayed radiation response may be manifested by enhanced vascular permeability, resulting in vasogenic edema. Such edema is usually clinically asymptomatic and an incidental finding on an MRI scan follow-up examination; it is commonly confined to the deep white
matter of the treated hemisphere in the region of the AVM. The edema can remain evident for up to 2 y and more, especially in the deep white matter, and slowly regress to a normal or near-normal state after a prolonged period. If massive edema is present, it may be asymptomatic, but it can cause transient or permanent neurologic impairment (Fig. 5); neurologic deficit can also occur as a consequence of a lesser amount of edema in sensitive and confined central brain structures. In such cases we have found that prompt treatment with corticosteroids has frequently arrested or reversed the process and associated neurologic deterioration. We have found that MRI scanning is the best imaging procedure for evaluating early and/or asymptomatic vasogenic edema and to assess the response to corticosteroid therapy. Irreversible neurologic damage can occur if the radiosurgical treatment induces occlusion of normal vessels and consequent focal infarction, especially in the deep central nuclei, internal capsule or brainstem.

Comparison of the clinical results of different radiosurgical modalities and clinical series in different centers is confounded by multiple variables and clinical judgments. These include patient selection criteria, AVM size and location, delineation of target volume, treatment dose, prior therapeutic intervention, duration of follow-up, threshold for classification of complications, and whether to include cryptic lesions in the series. Few series are sufficiently large to evaluate these parameters in relation to clinical outcome. About 30% of all patients referred to our clinical research program are not selected for treatment with radiosurgery, because their symptoms are not of sufficient magnitude or our protocol recommends surgical resection. Many patients have had surgery or embolization prior to radiosurgery; this may modify the risk of injury to the brain from subsequent high-dose radiation [15]. Out of nearly 500 referrals to our program of patients of all ages, only one has been declined radiosurgical treatment on the basis of excessive size of the AVM; extensive involvement of brain parenchyma throughout one entire hemisphere precluded treatment.

Meaningful comparison of results and treatment outcomes among various clinical series now requires the establishment of common measurable parameters of neurologic and neuroradiologic studies based on defined protocols. We consider the results in this series of young patients to be favorable. Stereotactic heavy-charged-particle radiosurgery has successfully obliterated a majority of AVMs, including some substantially larger than would be amenable to currently available photon irradiation techniques, while effecting satisfactory radiation protection of adjacent brain structures. The complications encountered in this series compare favorably with the potential risks of surgical intervention or the spontaneous
risk of progressive neurologic deficit in this patient group [10].

CONCLUSIONS

Considerable clinical research is required to define more precisely the selection criteria for stereotactic radiosurgery, and to assess the appropriate role of embolization in those patients who will undergo radiosurgery for deep, surgically-inaccessible intracranial AVMs. The optimal dose must be determined for radiosurgical treatment of AVMs in various locations within the brain, in order to improve the cure rate, protect against future intracranial hemorrhage and minimize potential adverse sequelae of the radiation treatment. At this time, we consider this method to be appropriate only for symptomatic surgically-inaccessible intracranial AVMs.
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FIGURE LEGENDS

Figure 1: Schematic diagram of charged-particle beam delivery system. The stereotactic patient positioning system allows translation along 3 orthogonal axes (x,y,z), and rotation about the y and z axes. The width of the high-dose Bragg ionization peak within the brain can be spread to the prescribed extent by interposing a modulating filter of comparable maximum thickness (x cm) in the beam path. The range in tissue of the Bragg peak region is determined by a range-modifying absorber. An individually-designed aperture shapes the beam in cross-section. Tissue-equivalent compensators adjust for skull curvature and further fine-tune the placement of the high-dose region. The ion chamber monitors the dose delivered in each beam. Multiple entry angles and beam ports are chosen with appropriate modification of parameters so that the high-dose regions of the individual beams intersect within the AVM target, with the lowest possible dose to sensitive adjacent normal brain structures.

Figure 2: Stereotactic heavy-charged-particle Bragg peak radiosurgery treatment plan for a 12-year-old girl with a brainstem AVM (defined by the inner ring of white dots). Isodose contours have been calculated at 10, 50, 80, and 100% of the maximum dose in axial (left) and coronal (right) planes. The 100% contour borders on the periphery of the lesion. There is a very rapid fall-off in dose outside the AVM target volume; very little normal brain tissue receives even as much as 10% of the dose to the AVM. There is virtually complete sparing and protection of midbrain and pontine structures. The helium-ion beam was collimated by an 8.5 x 11.5 mm elliptical brass aperture. Treatment was performed using 4 ports in 1 day to a volume of 300 mm$^3$ (dose, 25 GyE).

Figure 3A: A 10-year-old boy with a history of subarachnoid hemorrhage from a large (volume, 26,000 mm$^3$) right frontal temporal AVM. Upper, cerebral angiograms (lateral and anteroposterior projections) show the size, shape, and site of the AVM and its feeding vessels originating from several branches of the right middle cerebral artery. Lower, cerebral angiograms (lateral and anteroposterior projections) 12 mo after stereotactic helium-ion Bragg peak radiosurgery (dose, 28 GyE) demonstrate complete obliteration of the AVM. The patient remains neurologically intact 2.5 y after treatment (cf Figure 3B). (From Fabrikant JI, Frankel KA, Phillips MH, Levy RP: Stereotactic heavy charged-particle Bragg peak

Figure 3B: Stereotactic helium-ion Bragg peak radiosurgery treatment plan for the AVM illustrated in Figure 3A. The helium-ion beam was collimated by 47x35 mm and 49x37 mm elliptically-shaped brass and cerrobend apertures. A dose of 28 GyE was delivered to the AVM (defined by the inner ring of white dots) using 5 ports in 2 days to a volume of 26,000 mm³. Isodose contours in the axial plane are calculated for 10, 30, 50, 80, and 90% of the maximum dose. The 90% contour borders precisely on the periphery of the lesion. Note the rapid dose fall-off to the 80% level, and that the 10% isodose contour completely spares and protects the contralateral hemisphere.

Figure 4A: A 6-year-old girl presented with progressive right hemiparesis from a large left thalamic AVM. Left, upper and lower, representative MRI scans in the axial and sagittal projections before treatment. Right, upper and lower, comparable axial and sagittal projections 16 mo after stereotactic helium-ion Bragg peak radiosurgery. A dose of 28 GyE was delivered to the AVM using 4 ports in 2 days to a volume of 12,000 mm³. The AVM has been almost completely obliterated. The thalamus has been preserved intact, and the patient’s neurologic status has stabilized (cf Figure 4B).

Figure 4B: Stereotactic helium-ion Bragg peak radiosurgery treatment plan for the AVM illustrated in Figure 4A. The AVM is defined by the inner ring of white dots. The helium-ion beam was collimated by a 31x29 mm brass and cerrobend aperture. Isodose contours are calculated for 10, 50, 80, 90 and 99% of the maximum dose in axial (upper) and coronal (lower) planes. The 90% contour borders precisely on the periphery of the lesion. There is very rapid dose fall-off; the 10% isodose contour virtually spares and protects the contralateral hemisphere.

Figure 5: Sequential MRI scans in a 15-year-old girl with a very large (volume, 26,000 mm³) left parietal AVM. A dose of 32 GyE was delivered to the AVM using 4 ports in 2 days. She developed progressive edema and mild right-sided hemiparesis, but improved markedly with corticosteroid therapy. Currently, only subtle neurologic dysfunction can be appreciated and the patient no longer requires steroids. Her AVM has been fully obliterated (see
text). **Upper (left),** before stereotactic heavy-charged-particle Bragg peak radiosurgery; **(middle),** 13 mo after treatment, demonstrating initial radiologic signs of white matter edema; **(right),** 20 mo after treatment, illustrating the mass effect at which time the initial signs of hemiparesis became clinically apparent. **Lower (left),** 24 mo after treatment, demonstrating beginning resolution of the edema associated with marked clinical improvement; **(middle),** 30 mo after treatment, with further resolution of edema; **(right),** 34 mo after treatment, at which time a very subtle right foot dorsiflexion weakness remained; this continues to show improvement.
<table>
<thead>
<tr>
<th>Patient No./Sex/Age (y)</th>
<th>Location</th>
<th>Volume (mm³)</th>
<th>Dose (GyE)</th>
<th>FX²</th>
<th>Clinical Follow-Up³</th>
<th>Radiologic Follow-Up ≥ 1 y</th>
<th>Follow-Up³</th>
<th>Post-Treatment Hemorrhage/Complication/Comment</th>
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</thead>
<tbody>
<tr>
<td>1/M/15</td>
<td>L thalamus</td>
<td>3,880</td>
<td>45</td>
<td>3</td>
<td>ProgND</td>
<td>Complete (A)</td>
<td>2</td>
<td>Other AVM hemorrhage at 39 mo</td>
</tr>
<tr>
<td>2/F/10</td>
<td>L caudate</td>
<td>265</td>
<td>45</td>
<td>2</td>
<td>Normal</td>
<td>Complete (M)</td>
<td>2</td>
<td>Surgery and embolization at 36 mo</td>
</tr>
<tr>
<td>3/M/12</td>
<td>L thalamus</td>
<td>470</td>
<td>45</td>
<td>2</td>
<td>Normal</td>
<td>Complete (A)</td>
<td>2</td>
<td>Partial target treated</td>
</tr>
<tr>
<td>4/M/18</td>
<td>L thalamus</td>
<td>3,500</td>
<td>45</td>
<td>2</td>
<td>FixedND</td>
<td>Minimal (A)</td>
<td>2</td>
<td>Symptomatic edema at 20 mo</td>
</tr>
<tr>
<td>5/M/10</td>
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<td>1,550</td>
<td>45</td>
<td>1</td>
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<td>Complete (A)</td>
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<td>Aneurysm hemorrhage at 16 mo</td>
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<td>3,500</td>
<td>45</td>
<td>3</td>
<td>Minimal (A)</td>
<td>Minimal (A)</td>
<td>2</td>
<td>Limited target treated</td>
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<tr>
<td>7/F/15</td>
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<td>45</td>
<td>3</td>
<td>LTF</td>
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<td>Normal</td>
<td>Partial (M)</td>
<td>2</td>
<td>AVM hemorrhage at 12 mo; limited target treated</td>
</tr>
<tr>
<td>9/M/11</td>
<td>L thalamus</td>
<td>14,000</td>
<td>25</td>
<td>3</td>
<td>FixedND</td>
<td>Complete (A)</td>
<td>2</td>
<td>Limited target treated</td>
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<tr>
<td>10/F/14</td>
<td>L parietal</td>
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<td>Complete (A)</td>
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<td>Limited target treated</td>
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<td>11/F/15</td>
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<td>32</td>
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<td>Complete (A)</td>
<td>2</td>
<td>Limited target treated</td>
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<td>Complete (A)</td>
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<td>Limited target treated</td>
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<td>13/M/14</td>
<td>R basal ganglia</td>
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<td>1</td>
<td>FixedND</td>
<td>Complete (A)</td>
<td>2</td>
<td>Limited target treated</td>
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<tr>
<td>14/M/11</td>
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<td>35</td>
<td>2</td>
<td>Normal</td>
<td>Minimal (A,M)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
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<td>28</td>
<td>1</td>
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<td>Minimal (A)</td>
<td>2</td>
<td>Limited target treated</td>
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<tr>
<td>16/M/16</td>
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<td>Minimal (A)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
<tr>
<td>17/M/12</td>
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<td>16,500</td>
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<td>1</td>
<td>Normal</td>
<td>Complete (A)</td>
<td>2</td>
<td>AVM hemorrhage at 12 mo; limited target treated</td>
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<td>19/F/16</td>
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<td>30</td>
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<td>20/F/8</td>
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<td>4,800</td>
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<td>28</td>
<td>2</td>
<td>FixedND</td>
<td>Traces (A)</td>
<td>2</td>
<td>AVM hemorrhage at 12 mo; limited target treated</td>
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<td>22/M/13</td>
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<td>Complete (A)</td>
<td>2</td>
<td>AVM hemorrhage at 12 mo; limited target treated</td>
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<td>23/F/16</td>
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<td>Complete (A)</td>
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<td>24/M/16</td>
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<td>Complete (A)</td>
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<td>25/M/15</td>
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<td>Complete (A)</td>
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<td>AVM hemorrhage at 12 mo; limited target treated</td>
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<tr>
<td>26/F/18</td>
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<td>1,700</td>
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<td>AVM hemorrhage at 12 mo; limited target treated</td>
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<td>AVM hemorrhage at 12 mo; limited target treated</td>
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<td>Complete (A)</td>
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<td>AVM hemorrhage at 12 mo; limited target treated</td>
</tr>
<tr>
<td>29/F/12</td>
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<td>1</td>
<td>FixedND</td>
<td>Minimal (A)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
<tr>
<td>30/M/15</td>
<td>L caudate, c. callosum</td>
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<td>2</td>
<td>Normal</td>
<td>Partial (A,M)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
<tr>
<td>31/F/16</td>
<td>L thalamus</td>
<td>13,600</td>
<td>20</td>
<td>2</td>
<td>Normal</td>
<td>Minimal (A)</td>
<td>2</td>
<td>Limited target treated</td>
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<tr>
<td>32/M/18</td>
<td>L occipitotemporal</td>
<td>3,200</td>
<td>20</td>
<td>1</td>
<td>Normal</td>
<td>Minimal (A)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
<tr>
<td>33/F/11</td>
<td>R basal ganglia</td>
<td>60,000</td>
<td>10²</td>
<td>2</td>
<td>Normal</td>
<td>Partial (A,M)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
<tr>
<td>34/M/10</td>
<td>R basal ganglia</td>
<td>30,000</td>
<td>15</td>
<td>2</td>
<td>Normal</td>
<td>Partial (A,M)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
<tr>
<td>35/F/17</td>
<td>R thalamus</td>
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<td>15</td>
<td>2</td>
<td>Normal</td>
<td>Partial (A,M)</td>
<td>2</td>
<td>Limited target treated</td>
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<td>36/M/6</td>
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<td>Normal</td>
<td>Partial (A,M)</td>
<td>2</td>
<td>Limited target treated</td>
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<tr>
<td>37/F/18</td>
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<td>20</td>
<td>2</td>
<td>FixedND</td>
<td>Minimal (A)</td>
<td>2</td>
<td>Limited target treated</td>
</tr>
</tbody>
</table>

Footnotes:
²FX=fractions
³Obliteration: Minimal=<50%; Partial=50-95%; Traces=>95% at 1 y (we expect these to progress to complete obliteration); Complete=100%; (A)=confirmed by cerebral angiography; (M)=confirmed by MRI
⁴Prog=progressive since treatment; Fixed=unchanged deficit from before treatment; Imp=improved deficit since treatment; ND=neurologic deficit; LTF=lost to follow-up
⁵A conservative dose of 10 GyE was delivered, because a very large volume of normal brain tissue was involved in the treatment of this AVM.
TABLE 2
Summary of Patients with Angiographically-Occult AVMs

<table>
<thead>
<tr>
<th>Patient No./Sex/Age (y)</th>
<th>Location</th>
<th>Volume (mm³)</th>
<th>Dose (GyE)</th>
<th>Fx</th>
<th>Clinical Follow-Up</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>38/M/14</td>
<td>Pons</td>
<td>1,200</td>
<td>20</td>
<td>1</td>
<td>ProgND</td>
<td>Sudden worsening of unknown cause 6-4 mo</td>
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<td>39/M/18</td>
<td>L frontal</td>
<td>5,700</td>
<td>20</td>
<td>2</td>
<td>Normal</td>
<td></td>
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<tr>
<td>40/M/13</td>
<td>Hypothalamus</td>
<td>15,200</td>
<td>10</td>
<td>2</td>
<td>FixedND</td>
<td></td>
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</table>

*Fx=fraction
†Prog=progressive since treatment; Fixed=unchanged deficit from before treatment; ND=neurologic deficit
### TABLE 3

<table>
<thead>
<tr>
<th>Clinical Manifestations* (40 Patients)</th>
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<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Other nonhemorrhagic neurologic symptoms or deficit</td>
</tr>
<tr>
<td>Aneurysm hemorrhage or formation</td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
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</table>

* Multiple categories for many patients
### TABLE 4
Pre-Radiosurgery Procedures* (40 Patients)

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<th>Procedure</th>
<th>Count</th>
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<tr>
<td>None</td>
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</tr>
<tr>
<td>Surgery on AVM/feeders</td>
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</tr>
<tr>
<td>Embolization of AVM</td>
<td>8</td>
</tr>
<tr>
<td>Aneurysm repair</td>
<td>5</td>
</tr>
<tr>
<td>Shunt placement</td>
<td>5</td>
</tr>
<tr>
<td>Hematoma evacuation or reservoir placement</td>
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</table>

* 7 patients had multiple procedures
TABLE 5

Neuroradiologic Follow-up

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<th>Cerebral Angiography</th>
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<tr>
<td></td>
<td>≤ 1 y ≥ 2 y</td>
<td>≤ 1 y ≥ 2 y</td>
</tr>
<tr>
<td>Complete obliteration</td>
<td>10 14</td>
<td>9 10</td>
</tr>
<tr>
<td>Almost complete</td>
<td>3 0</td>
<td>2 0</td>
</tr>
<tr>
<td>obliteration (&gt; 95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial obliteration</td>
<td>7 2</td>
<td>4 2</td>
</tr>
<tr>
<td>(50-95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal obliteration</td>
<td>5 2</td>
<td>4 1</td>
</tr>
<tr>
<td>(&lt; 50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>25 18</td>
<td>19 13</td>
</tr>
</tbody>
</table>
Figure 1

Charged Particle Beam Delivery System

Stereotactic Coordinates (Planes)

Stereotactic Frame

Immobilizing Mask

x cm

AVM Target

Beam-Shaping Aperture

Tissue Equivalent Compensator

Range Modifying Absorber

Charged-Particle Beam

Bragg Peak Width Modulator (Propeller)

Ion Chamber

x cm

Angle of Rotation About y Axis

y

180°

Head Rotator

Turntable

Beamb Path

AVM Target
Figure 2

[Image of a medical scan with isodose contours and annotations]
Figure 3B
Figure 4A
Figure 4B