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HEAVY-CHARGED-PARTICLE RADIOSURGERY FOR
INTRACANIAL ARTERIOVENOUS MALFORMATIONS¹

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Running Head: Heavy Charged-Particle Radiosurgery

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Abstract: We have treated over 400 patients with symptomatic inoperable intracranial arteriovenous malformations with stereotactic heavy-charged-particle Bragg peak radiosurgery at the University of California, Berkeley in a collaborative program with Stanford University Medical Center and the University of California Medical Center, San Francisco. A long-term dose-searching clinical trial protocol has been developed and we have followed more than 270 patients for more than 2 years. Initially, radiation doses ranged from 45 to 35 GyE were used; currently, doses of 25 to 15 GyE are being evaluated. The characteristics of charged-particle-beams provide a relatively homogeneous dose distribution with the 90% isodose contour to the periphery of the lesion. When the entire arterial phase of the AVM core is included in the treatment field, the rates for complete obliteration 3 years post-treatment are: 90-95% for volumes $\leq 4 \text{ cm}^3$; 90-95% for volumes $> 4 \text{ cm}^3$ and $\leq 14 \text{ cm}^3$; 60-70% for volumes $> 14 \text{ cm}^3$. The total obliteration rate for all volumes up to 70 cm^3 is approximately 80-85%. The clinical grades at 2 years were excellent or good in 90%, poor in 5%, and progression of disease or died in 5%. For complete radiation-induced obliteration there is a relationship of dose and volume primarily, and location secondarily. Results on relationships between dose, AVM obliteration, and complications and sequelae of the radiosurgical procedure, and future directions for research in dose delivery and dose localization are presented and discussed.

Key Words: Heavy-charged-particle beams, intracranial arteriovenous malformations, stereotactic radiosurgery

Introduction

The potential for heavy-charged particle Bragg peak irradiation as a therapeutic method for producing discrete focal and lamellar lesions in the brain is derived from the clinical observations that the procedure avoids the morbidity and mortality associated with extensive neurosurgical procedures and that alternative methods, such as cryosurgery, electrothermal surgery and X-rays, provide poor spatial definition and lack of reliability in confining the reaction of the brain to radiation injury [1]. At the University of California at Berkeley - Lawrence Berkeley Laboratory (UCB-LBL) we have developed stereotactic heavy-charged-particle Bragg peak radiosurgery for treatment of symptomatic surgically-inaccessible intracranial arteriovenous malformations (AVMs) [1-10]. Narrow beams of accelerated helium ions are directed stereotactically to defined intracranial targets. The precision of our treatment planning and beam delivery system assures superior dose localization and dose distribution of the Bragg ionization peak throughout the AVM, generally with little or no neurovascular or parenchymal injury to adjacent critical brain structures. We have thus far treated over 400 patients, including 52 patients 18 years or younger, at the (UCB-LBL) heavy-charged-particle accelerators, initially at the 184-inch synchrocyclotron and currently at the Bevatron. This paper discusses the radiosurgical method, treatment planning, clinical results, complications, and certain future directions of the clinical program.

Method

The 230 MeV/amu and 165 MeV/amu helium-ion beam-line configurations at the 184-inch synchrocyclotron and Bevatron, respectively, have been reliably tested for stereotactic cerebral irradiation with the Bragg ionization peak [4]. In the standard configuration at the Bevatron the helium-ion beam-line has a range of about 15.0 cm to the distal edge of the unmodified Bragg peak, with very sharply delimited lateral and distal borders. This range of the beam is decreased to the desired value by the insertion of a

computer-controlled water-column absorber in the beam path (Figure 1). For clinical applications, the charged-particle beam can be shaped to conform to the configuration of the AVM and to any diameter from less than 6 mm to over 60 mm. Physical dose measurements indicate an unmodified Bragg peak-to-plateau ratio of about three, i.e., the physical dose to tissue is approximately three times greater in the Bragg ionization peak than in the plateau region of the beam. The beam is modulated to adapt to a variety of radiosurgical conditions; the modified Bragg ionization curve and its transverse profile for stereotactic radiosurgery will vary depending on a number of factors, including the size, depth and location of the lesion within the brain.

The primary advantage of narrow beams of heavy-charged-particles in radiosurgical treatment deep within the brain is the ability to confine the high-dose region to the desired volume of targetted tissue (see Figures 2 and 3). The 80% Bragg peak width along the unmodulated beam path is less than 3 mm, but can be spread out to any desired width to approximately 50 mm or more using specially-designed water-absorber modulation, and by stacking a number of mini-spread beams; this is essential to match the width of the Bragg peak to the intracranial target. The nuclear charge and mass of the helium ion are larger than those of the proton; therefore, the undesirable physical characteristics of multiple scattering and the range straggling with helium ions are less than for protons for the same range in tissues, resulting in a sharper focal beam for stereotactic radiosurgery [4]. The improved physical dose distributions with heavy-charged-particles are made possible by the relatively small amount of multiple scattering and range straggling and by the rapid fall-off of dose with depth beyond the end of the Bragg peak. These same physical characteristics require a stringently accurate assessment of, and compensation for, inhomogeneities in the tissue in order to accomplish precision radiosurgery.

The *radiosurgical procedure* for treatment of intracranial AVMs is designed to deliver a focal charged-particle beam to irradiate the main arterial feeders and abnormal shunting vessels of the AVM proper and to include, as completely as possible, the whole cluster of pathological shunting vasculature (AVM *core*) within the radiation field [9,10]. This entire vascular unit must be included in the target volume, and an optimal therapeutic

situation is present when the entire AVM core can be covered by a sufficient and uniform radiation dose. The reaction of the pathological tissue to radiation injury ultimately leads to progressive intravascular thrombosis and obliteration of the AVM shunts. The biological basis for this change involves injury to the vascular endothelial cells and their supporting biochemical architecture, cell and tissue repair, intimal proliferation, media degeneration, altered structure and function enhancing coagulation at the injured site, and thrombosis.

Treatment Planning

Treatment planning for stereotactic heavy-charged-particle radiosurgery for AVMs integrates anatomical and physical information from the stereotactic cerebral angiogram, and the stereotactic CT scans and MR images for each individual patient using computerized treatment-planning calculations for isodose contour display [3,4,10]. The data are used for three-dimensional target contouring and calculation of relative stopping power values from CT data, for desired dose distribution and dose localization. Multiple-entry angles and beam ports are chosen and contoured apertures and compensators are fabricated to conform the high-dose Bragg ionization peak to the contoured target of the AVM. Head immobilization is achieved with an interlocking thermoplastic mask fixed in the stereotactic frame which are integral components of the system's patient-positioning apparatus, the Irradiation Stereotactic Apparatus for Humans (Figure 1). The medical facility at the Bevatron and the stereotactic positioning system are designed so that the helium-ion beam path is coincident with the stereotactically-determined isocenter of the patient-positioning apparatus [1,3].

The dose to the central axis of the AVM, the aperture shape and size, the tissue-equivalent compensators, the number of beam ports, the angles for beam delivery and the range and modulation of the Bragg peak all determine the isodose contour configurations. Currently, total doses up to 25 GyE, applying an RBE of 1.3 for the helium-ion spread Bragg peak, are delivered to intracranial treatment volumes ranging from 0.1 cm³ to 70 cm³. In the initial stages of our dose-searching protocols, doses of 35 to 45 GyE were

used. Since AVM obliteration occurred at the lower dose levels of each protocol group, we lowered the doses delivered incrementally. At present, we have found that the optimal dose inducing obliteration of the AVM with the lowest risk of neurological sequelae depends on a number of factors and appears to lie in the range of 15 to 25 GyE, using the helium-ion Bragg peak [5,6,9,10]. Dose selection depends on size, shape and location of the AVM within the brain and a number of other factors including the total volume of normal brain that must be traversed by the plateau portion of the charged-particle beams. The average treatment volume for most patients ranges from 1.5 cm³ to 16 cm³. Most often treatment occurs through 3 to 5 entry portals, most frequently 4 noncoplanar beams, and is delivered daily in 1 or 2 days, depending on the treatment volume (e.g., in 1 day if the volume is 4 cm³ or less) and the volume of normal brain tissue traversed by the plateau beam. The dose to the critical normal brain structures adjacent to the AVM is considerably less than the dose to the target volume, because fall-off to 10% of the central dose occurs within 4 to 6 mm, and is within 2 to 3 mm along the lateral margins of the beam (Figures 2 and 3).

Clinical Results

The objective of the radiosurgical procedure is to induce limited radiation injury to the abnormal AVM shunts leading to intravascular coagulation, and thereby achieve changes in the intracerebral hemodynamic condition, resulting in reduction or elimination of subarachnoid or intraparenchymal brain hemorrhages with their associated morbidity and mortality, decrease in progressive or fixed neurological deficits, lower frequency of seizures, and fewer subjective complaints, including frequency and intensity of headaches [1,6,9,10]. Nearly all patients have received clinical and neuroradiological follow-up evaluations frequently since treatment; about three-quarters of the patients have had 5-year followup review, and extended review to 10 years has now been done on a regular basis where feasible. Observations in all patients, both adults and children, thus far treated indicate that the clinical objectives are being achieved in the majority of patients. The first 270 patients have been evaluated clinically to mid-1990; using the Drake *clinical grading*

[6], about 85-90% of the patients have *excellent* or *good* neurological clinical grade, about 5% have *poor* neurological clinical grade, and 5% have had progression of disease and *died*, or died as a result of unrelated intercurrent illness [6,10]. In our UCB-SUMC patient series, we examined 101 consecutive patients to 6 years of follow-up. The final health outcome was *excellent* in 58% and *good* in 36% of patients (Table 1) [6]. Seizures improved in 63% of patients, headaches in 68% and neurological deficit in 27%. Progressive neurological deficit stabilized in 55%.

Cerebral angiography illustrates changes in vessels and shunts at intervals following stereotactic radiosurgery for angiographically-demonstrable AVMs. Hemodynamic changes are manifested by a time-dependent decrease in blood flow through the pathological cluster of shunts and a decrease in size of the feeding arteries, shunts and draining veins. Anatomical changes include progressive decrease in the size of the AVM until stabilization or total disappearance occurs. The hemodynamic changes occur successively and are usually observed before the anatomical changes. Neuroradiological followup to the end of 1990 indicate overall that for complete angiographic obliteration 3 years after treatment the obliteration rates are : 90-95% for volumes $<4 \text{ cm}^3$; 90-95% for volumes $\geq 4 \text{ cm}^3$ and $\leq 14 \text{ cm}^3$; and 60-70% for volumes $>14 \text{ cm}^3$; for all volumes up to 70 cm^3 it is approximately 80-85% after 3 years [6,7]. Our UCB-SUMC clinical series showed an overall complete malformation obliteration rate of 29% at 1 year, 70% at 2 years, and 92% at 3 years following helium-ion irradiation (Table 2) [6]. The rate and extent of AVM obliteration appear to be threshold phenomena directly related to treatment volume and dose. Malformations smaller than 4 cm^3 (2 cm diameter) thrombosed more rapidly and more completely (94% complete obliteration at 2 years, 100% at 3 years) than larger lesions. Intermediate-sized malformations (2 cm to 3.7 cm diameter) had an obliteration rate of 75% at 2 years and 95% at 3 years, while the larger lesions ($>3.7 \text{ cm}$ diameter) had an obliteration rate of 39% at 2 years and 70% at 3 years. Obliteration occurred most completely in the high-dose (30 to 45 GyE) group of patients, and occurred at the lower dose levels in each group in the dose-searching protocols. In our UCB-SUMC patient series, this also occurred in the intermediate dose group; 24 to 28 GyE proved to be

quite effective (Table 3). Following complete angiographic obliteration, we have not seen subsequent angiographic reappearance of the malformation, even when prior embolization was performed.

Figure 4 illustrates the cerebral angiograms of a patient with recurrent seizures and progressive motor and sensory changes resulting from a deep right frontal-temporal AVM. The high-volume, high-flow AVM and the feeding vessels arising from branches of the right middle cerebral artery result in a profound vascular steal; the anterior cerebral artery and its branches do not fill. One year after stereotactic radiosurgery (dose, 35 GyE; volume, 3.7 cm³), there was complete obliteration of the AVM; redistribution of the normal cerebral blood flow with filling of the anterior and posterior cerebral arteries and their branches and was associated with a reversal of the vascular steal phenomenon.

Complications

From the followup available we can conclude that by stereotactic heavy-charged-particle Bragg peak irradiation of the feeding arteries and shunts, total and irreversible angiographic obliteration of deep AVMs is possible in a large number of patients, and protection against hemorrhage with reduced morbidity and mortality occurs in over 80% of patients. Complications are scored very conservatively; any definite or possible sequelae of radiosurgery are considered to be complications, even if functional impairment is minimal or temporary. Some neurological dysfunction occurred in 15% of patients, nearly all in the earlier high-dose group. More than half of these patients have had complete or nearly complete return to their preradiosurgery condition. The complications associated with radiation injury include vasogenic edema and vasculopathy; neurological sequelae may be categorized as *major* (e.g., hemiparesis, cranial nerve palsies) and *minor* (e.g., visual field deficit, mild paresis). The rate of permanent major complications combined is approximately 10-11%, but this is confined almost completely to the high-dose treatment group (30 to 45 GyE) treated in the initial stages of the dose-searching protocol. In the most recent clinical follow-up and analyses, no complications appear to occur at doses less

than 25 GyE [6]. However, even at these complication rates, the cure rates are relatively high in this high-risk patient population, and the serious complications encountered may be considered acceptable in view of the potential for spontaneous intracranial bleeding and profound neurological sequelae, morbidity and mortality, associated with the natural history of this disease in untreated patients [9,10]. There has been no immediate treatment morbidity, and no deaths have occurred from the radiation procedure.

Conclusions

Based on long-term neuroradiological evaluation using cerebral angiography, CT and MR imaging in all patients, and PET and radioisotope scanning of selected patients, together with extensive clinical neurological followup, it appears that stereotactic heavy-charged-particle Bragg peak radiosurgery obliterates high-flow intracranial AVMs and protects against further intraparenchymal brain hemorrhage with reduced morbidity and no treatment-associated mortality. The current procedure still has two major disadvantages, viz., the prolonged latent period and the relatively low but finite incidence of major neurological complications. We consider the procedure only for selected patients with symptomatic intracranial AVMs in whom the potential surgical risk is considered unacceptably high, and patient selection and treatment are constrained by specifically-defined multi-institutional patient protocols.

Future Directions

One advance in dose localization for realizing the clinical advantages of heavy-charged-particle beams is the development of a dynamic beam delivery and beam spreading system that allows modulation of the spread Bragg peak over the target volume for implementing of three-dimensional conformal therapy for intracranial vascular disorders and tumors. Such a system improves the therapeutic efficacy of the delivered beams, and increases the versatility of the beam spreading system for various clinical situations. Our

aim has been to test the hypothesis that therapeutic irradiation with heavy-charged-particle beams will improve clinical results for a significant number of patients than will conventional radiation.

The radiation dose that can be delivered to an intracranial target volume, in general, is limited because of the critical normal brain tissues in the high-dose volume (the volume that receives the same dose as the AVM or tumor), and other critical normal tissues which are elsewhere in the irradiated volume. Charged-particle beams, because of their Bragg ionization peaks, have been used to treat intracranial targets at a number of different sites with less morbidity than with conventional photon irradiation. Although the Bragg peaks of the heavy-charged-particle beams and their favorable peak-to-plateau ratios can be used to produce dose distributions superior to those attainable with other types of radiation, the heavier ions always impart some dose distally (in the *tail* of the Bragg peak) the target volume and a significantly smaller dose proximally (in the *plateau* of the Bragg curve) to the target volume. The standard procedure to achieve the desired dose uniformity throughout the target volume by a given beam has been to modulate the range of the beam with some sort of variable thickness absorber (*fixed* modulation). The restriction of using the same modulation for all rays within the beam results in delivering a greater dose than necessary to tissues in those regions where the target thickness is less, with some regions receiving the same dose that is being delivered to the target. In spite of this limitation, improvements in treatment through the use of the charged-particle beams have been possible mainly by the reduction (when compared to external photon therapy) of the high-dose volume and the dose to structures in the remaining irradiated volume. The implementation of a *variable* modulation beam delivery system may result in significant reduction in the integral dose. Such improvements to the dose distributions will offer improved tolerance to treatment and may allow an increase in the effective target or tumor dose with a resulting increase in the probability of cure or control.

For this purpose, a raster scanning system with *variable* modulation capability has been developed at Lawrence Berkeley Laboratory. With this system, the treatment volume may be divided into many layers, and scanned layer by layer starting from the distal surface

and progressing toward the proximal portion by shortening the residual range of the beam. The Bragg peak is spread out to a moderately wide 'mini-spread' beam of approximately 1-cm width, and axially stacked by changing the range. The contours of the proximal and distal surfaces of the target volume are usually smaller than the widest lateral extent; and, as the axial stacking proceeds, the aperture of the variable collimator is reduced in such a way that normal tissues adjacent to the target volume are protected from unwanted Bragg peak radiation. The axial stacking method delivers uniform doses into a target volume with varying widths of the Bragg peak using a raster scanner, a variable collimator and a compensator. For proton and helium-ion radiation which produce no or few fragments, the Bragg curves do not exhibit a tail dose (the dose due to the fragments beyond the distal edge of the Bragg peak); therefore, the method produces very satisfactory dose distributions.

We plan to utilize this beam spreading system to take advantage of the dose localization properties of heavy-charged-particle beams. It can be anticipated that the improved dose localization due to the variable modulation will allow greater target volume doses with reduced doses in the surrounding normal tissues, resulting in reduced complication rates with increased probability of cure or local control. New clinical trials for intracranial sites are expected to be started when dynamic beam delivery system is fully implemented. It is our belief that heavy-charged-particle beams combined with dynamic beam delivery and raster scanning, will allow improved dose distribution and dose delivery of localized irradiation in the central nervous system. It can be expected that many of the large and complexly-formed intracranial AVMs and brain tumors, small lesions, such as pituitary microadenomas, brain stem gliomas, isolated brain metastases and similar intracranial disorders can now be approached successfully. Furthermore, localization of very discrete focal lesions can be achieved in vital brain centers to treat certain diseases, such as Parkinson's disease, or for the control of pain, and for such conditions as brain-stem cryptic angiographically-occult vascular malformations in children.

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Figure-legends

Fig. 1. The charged-particle beam delivery system for stereotactic radiosurgery of intracranial vascular disorders at the UCB-LBL 184-inch synchrocyclotron. The stereotactic patient positioning system (ISAH) permits translation along 3 orthogonal axes and provides patient immobilization and positioning at the isocenter. The width of the Bragg ionization peak is spread by interposing a modulating filter in the beam path. At the Bevatron accelerator, the Bragg peak is modulated by use of a computer-controlled variable-position water column absorber. The range in tissue of the Bragg peak region is determined by a range-modifying absorber. An individually-designed aperture tailored to the lesion shapes each beam in cross section; tissue-equivalent compensators adjust for skull curvature and tissue inhomogeneities. The dose delivered by each beam is monitored with an ion chamber. Multiple entry angles and beam ports are chosen so that the high-dose regions of the individual beams intersect and stop within the defined target with the lowest dose to adjacent normal brain tissues (adapted from [5]).

Fig. 2. Stereotactic helium-ion Bragg peak radiosurgery treatment plan for a 38-year-old woman with an AVM in the brain stem (defined by the inner ring of white dots). Isodose contours are shown superimposed on a central CT scan. The helium-ion beam was collimated by an 8 mm circular aperture; treatment was performed using four coplanar ports in 1 day to a volume of 0.25 cm^3 within the brain stem (dose, 45 GyE).

Fig. 3. Stereotactic helium-ion Bragg peak radiosurgery treatment plan for a 39-year-old man with a large left temporal and deep central AVM. The helium-ion beam was collimated by two individually-shaped brass and cerrobend apertures; 25 GyE was delivered to the lesion (defined by the inner ring of white dots) using seven noncoplanar ports in 2 days to a volume of 54 cm³. The 90% contour borders precisely on the periphery of the lesion. There is a rapid dose fall-off to the 70% level, and the 10% isodose contour completely spares and protects the contralateral hemisphere.

Fig. 4. A 39 year-old woman with a right frontal-temporal AVM. *Upper:* Cerebral angiograms show the size, shape and location of the AVM and its feeding vessels originating from the right middle cerebral artery and associated with a severe vascular steal. *Lower:* Cerebral angiograms 1 year after helium-ion Bragg peak radiosurgery (dose 35 GyE; volume, 3.7 cm³) demonstrate complete obliteration of the AVM. There has been complete reversal of the vascular steal with return of normal regional cerebral blood flow patterns. The patient remains neurologically intact 8 years after treatment.

Table 1
Clinical Grade at Last Follow-up in 101 Patients⁺

Presenting Clinical Grade	Excellent	Good	Poor	Dead
<u>Excellent</u> 68	53 (78%)	12 (18%)	2 (3%)	1 (1%)
<u>Good</u> 29	5 (17%)	21 (72%)	2 (7%)	1 (3%)
<u>Poor</u> 4		1 (25%)		3 (75%)
<u>All Grades</u> 101	58 (57%)	34 (34%)	4 (4%)	5 (5%)

+ adapted from [6]

Table 2

Stereotactic Radiosurgery Results at 3 Years (230 Patients)

AVM Volume (cm ³)	% of Patients	Obliteration Rate
≤4	49%	90-95%
>4 and ≤14	33%	90-95%
>14	18%	60-70%
All Volumes	100%	80-85%

Table 3

Complete AVM Obliteration vs. Treatment Dose⁺

Dose (GyE) ⁺⁺	1 Yr	2 Yr	3 Yr
11.5 - 20	4 / 18 (22%)	6 / 10 (60%)	6 / 6 (100%)
24 - 28	5 / 23 (23%)	17 / 23 (74%)	19 / 21 (90%)
30 - 45	9 / 16 (56%)*	16 / 18 (89%)**	18 / 19 (95%)

* p = 0.057

** p = 0.008

⁺⁺ RBE = 1.3

⁺ adapted from [6]

Charged Particle Beam Delivery System

Figure 1

XBL 8810-7674

XBB 853-1740

Figure 2

XBB 878-6973A

Figure 3

XBB 853-2094

Figure 4

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