Stereotactic Radiosurgery

The Role of Charged Particles

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Stereotactic radiosurgery using charged-particle beams has been the subject of biomedical research and clinical development for more than 50 years. Charged particles of proton mass or greater manifest unique physical properties that can be used to place a high dose of radiation preferentially within the boundaries of a deeply located intracranial target volume. Since 1954, nearly 10000 patients have been treated using this technique. Treated disorders include pituitary tumors, vascular malformations, primary and metastatic brain tumors, and subfoveal neovascularization. Charged-particle radiosurgery is particularly advantageous for the conformal treatment of large and/or irregularly shaped lesions, or for the treatment of lesions located in front of or adjacent to sensitive brain structures.

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The application of charged-particle radiation to stereotactic radiosurgery has been the subject of biomedical research and clinical development for more than 50 years (1, 2). In 1946, Wilson (3) first proposed the clinical use of charged-particle beams because of their unique physical properties. After completion of the 184-inch synchrocyclotron at the University of California at Berkeley, Lawrence Berkeley Laboratory in 1947 (4), Tobias and colleagues (5) began studies of the biologic effects of small beams of protons, deuterons and helium ions. Particular attention was paid to the reaction of normal brain tissues to charged-particle irradiation for subsequent clinical application to radiosurgery (6).

The range of medical applications was constrained initially by the limitations of available neuroradiologic techniques for stereotactic localization, image correlation and treatment planning (2). Early clinical trials were therefore restricted to selective destruction of small, well-defined target volumes that could be localized accurately by existing neuroradiologic procedures. Stereotactic irradiation of the pituitary gland was among the earliest applications, because localization of the sella turcica could be accomplished reliably with plain radiographs. In 1954, the first clinical radiosurgical procedures using charged particles were performed for pituitary hormone-suppression treatment of metastatic breast cancer (7, 8). Charged-particle radiosurgery was then applied to the pituitary-ablation treatment of proliferative diabetic retinopathy (9), and to the treatment of pituitary adenomas (10, 11). With the development of improved techniques of stereotaxis and cerebral angiography, charged-particle radiosurgery was applied to the treatment of arteriovenous malformations (AVMs) (12–14). More recently, the advent of high-resolution computed x-ray tomography (CT) and magnetic resonance imaging (MRI) has made it possible for these techniques to be used for a wide variety of primary and metastatic intracranial tumors. As of 1998, nearly 10000 patients worldwide have been treated with charged-particle radiosurgery.

PHYSICAL PROPERTIES OF CHARGED-PARTICLE BEAMS

Charged-particle beams of proton mass or greater (e.g., helium, carbon, and neon ions) manifest unique physical properties, first observed by Bragg in 1904 (15), that can be used to place a high dose of radiation preferentially within the boundaries of a deeply located intracranial target volume (Fig. 1) (2). These include: (a) a well-defined range that can be modulated so that the beam stops at the distal edge of the target, resulting in little or no dose beyond the target; (b) an initial region of low dose (the plateau) as the beam penetrates through matter, which is

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followed by a region of high dose (the Bragg peak) at the end of the range of the beam and deep within the tissue and which can be adjusted to conform to the length of the target so that the entrance dose can be kept to a minimum; and (c) very sharp lateral edges that can readily be made to conform to the projected cross-sectional contour of the target so that little or no dose is absorbed by the adjacent normal tissues.

The distance or range that a beam of monoenergetic charged particles travels in tissue before stopping is a function of the charge and kinetic energy of the particle and the physical characteristics of the absorbing tissue. Naturally occurring charged particles (e.g., alpha particles emitted from radon progeny, radium, or the transuranic elements) generally have fairly low energies (about 5 MeV/u for these alpha-emitting radionuclides), and therefore a range in tissue of about 50 to 100 μm (i.e., only a few cell diameters). However, specially designed particle accelerators are able to produce monoenergetic beams consisting of charged particles of very high energy and ranges in tissue of up to 30 cm or more. The effective range in tissue can be modified precisely or modulated to specification by interposing absorbing filters of appropriate design or thickness in the beam path, providing considerable flexibility of choice of beam direction for stereotactic treatment planning (16).

The absorbed radiation dose is, in part, a function of the rate of a charged particle's energy transfer to the tissues

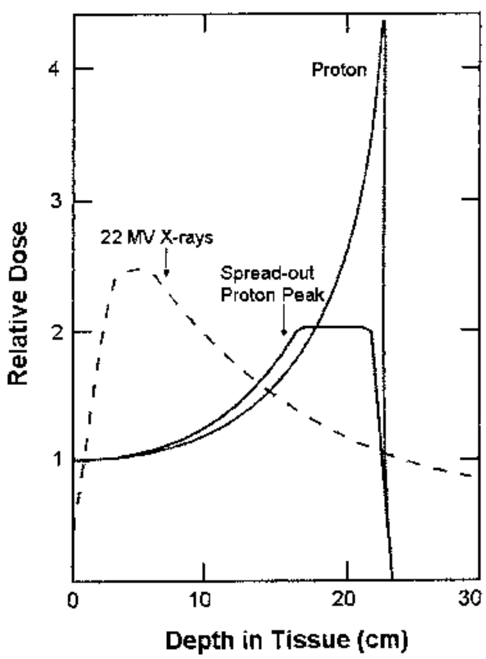

Fig. 1. Relative dose as a function of depth in tissue is shown for 22 MV x-rays, an unmodulated proton-beam plateau and Bragg ionization peak, and a spread-out proton Bragg peak modulated by absorbing filters in the beam path.

through which it passes. The radiation dose absorbed is nearly constant during the first portion of the particle's path (the plateau ionization region) but increases rapidly just before the particle slows down and stops, resulting in a large local energy deposition in the Bragg ionization peak (Fig. 1). The unmodulated Bragg peak is extremely sharp, just a few millimeters in width in tissue, and therefore too narrow for the treatment of many intracranial lesions. However, the width of the Bragg peak can be spread to 50 mm or more in the direction of the beam by interposing variable thickness absorbers in the beam path and by adding together or stacking a series of beams of slightly different ranges.

Charged-particle beams are readily collimated by metal apertures, such as brass and certain alloys, to conform to the cross-sectional size and shape of the target volume in any projection. Photons (e.g., x-rays from a linear accelerator or gamma rays from a cobalt-60 source) also can be collimated to match the cross-sectional beam shape to the target in any given projection, but this is difficult to accomplish in practice because a large number of discrete beams with different entry angles or continuous radiation arcs are required to approximate the excellent dose distributions that can be obtained with only a few (three to five) charged-particle beams (17). Each charged-particle beam can be directed stereotactically to place an individually shaped three-dimensional high-dose region precisely within the brain by adjusting the range, spreading the Bragg peak, introducing tissue-equivalent compensators, and using an appropriately shaped aperture. Several entry angles and coplanar and/or noncoplanar beam ports are directed stereotactically so that the high-dose regions of the individual beams intersect within the target volume. This approach results in a much lower dose to immediately adjacent and intervening normal brain tissues.

DOSE-VOLUME HISTOGRAM ANALYSIS

Methods for comparison of different irradiation techniques for radiotherapy and radiosurgery of the different tissues and organs of the body have been developed and applied to currently used stereotactic radiosurgical procedures for the treatment of intracranial lesions (17). Three-dimensional treatment planning calculations are used to compare the dose distributions for various types of radiation and different radiation geometries by means of dose-volume histograms and integral doses to the target volume and to normal brain. The radiation doses to normal brain structures adjacent to and remote from the target volume have been demonstrated to be relatively low with stereotactic charged-particle Bragg peak radiosurgery when compared to photon irradiation techniques that use focused beams of x-rays or gamma rays; this difference becomes especially marked in the treatment of larger intracranial lesions (Fig. 2).

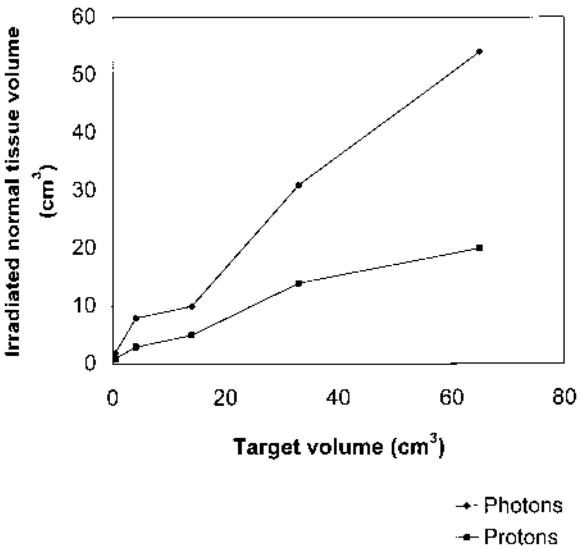

Fig. 2. The volume of brain tissue (cm^3) outside the target volume that receives 80% or more of the dose delivered to the target volume plotted as a function of target volume (cm^3). These data are derived from dose-volume histograms for defined target volumes using photon irradiation (cobalt-60 gamma rays or x-ray) and proton (155 MeV/u) irradiation for stereotactic radiosurgery of target volumes ranging from 0.5 to 65 cm^3. Treatment plans were designed to place the 90% isodose line at the lesion periphery. Spheres of 1, 2, 3, 4, and 5 cm diameter correspond to volumes of 0.5, 4.1, 14, 33, and 65 cm^3, respectively. From the smallest to the largest volumes examined, focused photon irradiation results in the irradiation of 2 to 3 times more normal brain tissue surrounding the target volume compared with proton irradiation (Adapted from reference (17)). ◆ = Photons; ■ = protons.

CLINICAL APPLICATIONS

A comprehensive review of the historical development of charged-particle radiosurgery, reported medical applications and clinical experience and results is beyond the scope of this review. Selected historically significant or representative studies have therefore been summarized and/or cited for further reference.

PITUITARY IRRADIATION

Stereotactic charged-particle radiosurgery of the pituitary gland has proved to be a highly effective method for treatment of a variety of endocrine and metabolic hormone-dependent conditions, alone or in combination with surgical hypophysectomy and/or medical therapy in more than 3500 patients worldwide. This includes patients with acromegaly, Cushing's disease, Nelson's syndrome and prolactin-secreting adenomas, and metastatic breast carcinoma and diabetic retinopathy. The objective has been to deliver a high dose to the tumor or the central core of the pituitary gland, while preserving a narrow rim of functional pituitary tissue. Treatment has resulted in reliable control of tumor growth and suppression of hypersecretion in a great majority of the patients. For example, mean serum growth hormone levels in a cohort of 234 patients with acromegaly treated with helium-ion radiosurgery decreased by nearly 70% in one year, continued to decrease thereafter, and remained normal throughout more than 10 years of follow-up (18). Similar results were found with proton radiosurgery for acromegaly (10), and for radiosurgical treatment of Cushing's disease and prolactinoma (2, 11). Variable degrees of hypopituitarism have occurred in as many as one-third of cases, but endocrine deficiencies have been readily corrected with appropriate hormone supplemental therapy. The reader is referred to references (2) and (19) for comprehensive reviews of this subject.

ARTERIOVENOUS MALFORMATIONS

Stereotactic charged-particle radiosurgery has been applied to the treatment of intracranial AVMs in nearly 3000 patients worldwide since 1965 (2, 13, 14, 16). While many AVMs are amenable to neurosurgical removal or endovascular embolization followed by surgery, surgical removal may involve high risks for the malformations located in deep or eloquent regions of the brain and for large lesions with multiple arterial supply or deep venous drainage. Moreover, these techniques, when possible, are not always completely successful because of the position or complexity of the vascular malformation. The object of radiosurgical treatment is to induce localized endothelial cell proliferation, vascular wall thickening, and thrombotic obliteration of the malformation while sparing normal adjacent brain structures.

The physical characteristics of charged-particle beams are uniquely advantageous for the radiosurgical treatment of AVMs. Bragg peak radiosurgery has the precision required to treat eccentric and irregular AVMs of very large size (Fig. 3), as well as to deliver extremely sharp focal beams accurately to small lesions (e.g., in the brain stem or central nuclei) while protecting the adjacent critical nervous tissues and the rest of the normal brain (Fig. 2) (1, 2, 16).

The most detailed report of charged-particle radiosurgery for AVM was that from the University of California at Berkeley–Stanford University collaborative program (14). Here, 86 consecutive AVM patients (47 females, 39 males) ranging in age at the time of treatment from 9 to 69 years (mean 33 years) were treated with helium-ion radiosurgery. Almost half of these patients (44%) had AVMs located in the brain stem, corpus callosum, thalamus, or basal ganglia, and most of the remainder had large malformations in critical areas of the cerebrum—the sensory, motor, language, or visual areas of the cortex. One-quarter of the AVMs were larger than 25 cm^3.

In an evaluation carried out 24–72 months (mean, 38 months) after radiosurgery, clinical outcome was graded as excellent in 58% and good in 36% of patients. In 63% of patients presenting with seizures and 68% of patients presenting with headaches there was an improvement in these symptoms. Two years after radiosurgery, complete angiographically demonstrated obliteration of the AVM occurred in 70%, partial closure (10% to 99% obliteration) occurred in 23%, and no change occurred in 7% of patients. Three years after treatment, 92% of patients had complete AVM obliteration, 4% had partial obliteration, and 4% experienced no change. The rate and extent of obliteration appeared to be a threshold phenomenon directly related to the AVM volume and the radiation dose. Smaller AVMs had higher rates of obliteration than larger ones ($p < 0.005$ after 1 and 2 years). AVMs smaller than 4 cm^3 became thrombotic more rapidly and more completely than larger lesions ($p < 0.05$ for the comparison with AVMs 4 to 25 cm^3 in volume and $p < 0.001$ for the comparison with those > 25 cm^3 (Cox test). Intermediate-sized AVMs were obliterated more rapidly and more completely than large AVMs ($p < 0.05$, Cox test). However, full obliteration was observed 3 years following radiosurgery in 70% of AVMs > 25 cm^3.

Preliminary results using stereotactic proton radiosurgery for AVMs at Loma Linda University Medical Center have paralleled the Berkeley-Stanford experience. Our emphasis was on the treatment of larger AVMs. Between December 1993 and April 1998, we treated 50 AVMs ranging from 10.7 to 120.8 cm^3 (37.5 ± 29.5 cm^3), generally in two daily fractions totalling 22.1 ± 2.7 GyE. Long-term follow-up is in progress.

MALIGNANT DISORDERS

At Loma Linda University Medical Center, protocols are being developed and implemented for stereotactic proton radiosurgery of brain metastases, boost treatment for primary glioblastoma multiforme (GBM), and treatment for GBM recurrences following conventional irradiation. In terms of the physical dose distribution, proton irradiation is associated with progressively favorable relative dose conformity with increasing lesion size, when compared

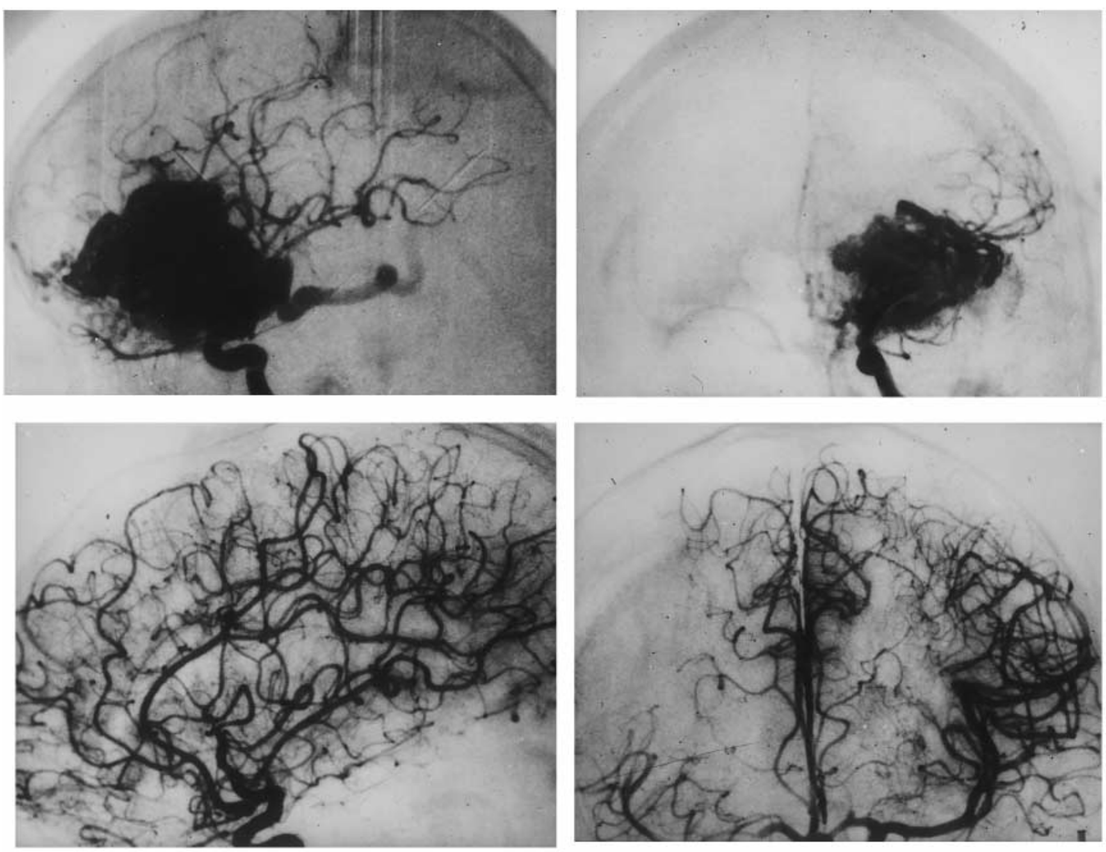

Fig. 3. Cerebral angiograms in a 23-year-old man with a history of refractory seizures from a large (40 cm^3) left frontotemporal AVM. Upper, Lateral and anteroposterior views of the internal carotid artery angiogram demonstrate the AVM supplied by branches of the anterior and middle cerebral artery circulations. The vascular steal is prominent. Lower, comparable view taken 18 months after helium-ion radiosurgery (dose, 28 GyE) demonstrates complete obliteration of the AVM. Normal cerebral blood flow has been restored, with marked reversal of the vascular steal. (From Levy RP, Fabrikant JL, Frankel KA, Phillips MH, Lyman JT. Charged-particle radiosurgery of the brain. Neurosurg Clin North Am 1990; 1:980, with permission.)

with photon irradiation (Fig. 2) (17). This relative conformity advantage may play an important role in the treatment of GBMs in particular, which often are quite large at the time of initial presentation or recurrence. The general therapeutic strategy has been to employ these advantageous physical dose-distribution properties of proton irradiation in combination with various dose fractionation schemes tailored to the size, location, and histology of the lesion, in order to optimize the therapeutic gain.

MACULAR DEGENERATION

Proton-beam irradiation for the treatment of the category of macular degeneration that is associated with subfoveal neovascularization has shown dramatically favorable initial results (20). The rationale for this treatment was based on the observed sensitivity to irradiation of proliferating endothelial cells in culture, and the relative resistance to irradiation of the retina and choroid. Proton irradiation is ideally suited for this task, since a satisfactory dose to the neovascular membrane can be delivered in a few minutes, using a single anterior oblique proton field to deliver a dose of 8 to 14 GyE. The proton beam stops without entering the brain or the opposite eye. When x-ray-based systems were employed for this task, the integral dose to adjacent tissues (e.g., brain, pituitary gland) increased by a factor of 20 as compared to proton irradiation (21). Preliminary results have shown that a dose of 14 GyE has been dramatically effective in halting visual loss, and with negligible side effects.

SUMMARY

Stereotactic charged-particle radiosurgery has now been successfully employed in for nearly 45 years in the clinical treatment of nearly 10000 patients. Treated disorders include pituitary tumors, vascular malformations, primary and metastatic brain tumors, and subfoveal neovascularization. Charged-particle radiosurgery can be applied readily to the treatment of small spherical or ovoid intracranial lesions. However, the unique physical properties of charged particles make this method particularly advantageous for the conformal treatment of large and/or irregularly shaped lesions, or for the treatment of lesions located in front of or adjacent to sensitive brain structures (e.g., subfoveal membranes).

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