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## Clinical Applications of Stereotactic Radiosurgery

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# CLINICAL APPLICATIONS OF STEREOTACTIC RADIOSURGERY[1]

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# INTRODUCTION

The concept of *stereotactic radiosurgery* was introduced in 1951 by Leksell [58] to describe a technique developed to create small, well-defined lesions in the brain using stereotactically-directed narrow beams of ionizing radiation. Stereotactic radiosurgery may be characterized as a clinical external-beam radiation-treatment procedure applied to a relatively small volume of intracranial tissue in which the total radiation dose is delivered stereotactically through multiple discrete entry portals or arcs in a single or limited number of fractions; the intent is to damage a designated population of cells within the target volume, while protecting the adjacent normal tissues (Table 1). The radiosurgical approach is contrasted with conventional external-beam radiotherapy, which generally involves treatment of a larger tissue volume in which the total dose is delivered in a relatively large number of small daily increments over a period of weeks; here, the intent is to destroy the reproductive capacity of neoplastic cells (Table 1).

For many years, the clinical experience in stereotactic radiosurgery was concentrated in a few research centers – primarily, the Karolinska Institute in Stockholm, the University of California at Berkeley - Lawrence Berkeley Laboratory (UCB-LBL), the Massachusetts General Hospital - Harvard Cyclotron Laboratory (MGH-HCL), the Burdenko Neurosurgical Institute in Moscow and the Institute of Nuclear Physics in St. Petersburg [24,61,110]. The earliest experimental applications of radiosurgery utilized supervoltage X-ray beams [57,58,60]. Subsequently, teams of investigators at specialized clinical radiosurgical-treatment centers developed methods to exploit more-energetic radiations, including accelerated charged particles [39,40,48,50,54,55,70], $^{60}$Co $\gamma$-rays [3,6,106] and, more recently, high-energy X-rays [8,14].

The range of medical applications was constrained initially by the limitations of available neuroradiologic techniques for stereotactic localization, image correlation and treatment planning [61]. Early clinical trials, therefore, were restricted to selective destruction

of small, well-defined intracranial target volumes that could be localized reasonably 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 using plain radiographs [61]. In 1954, the first stereotactic irradiation procedures utilizing charged particles in clinical patients were performed at UCB-LBL for pituitary hormone suppression in the treatment of metastatic breast carcinoma [16,50,54,114,115]. Shortly thereafter, pituitary radiosurgery was applied to the pituitary-ablation treatment of patients with proliferative diabetic retinopathy [39,55,69] and to the treatment of pituitary adenomas [2,40,68,70]. During these early years, limited numbers of patients were also treated for other conditions, including certain functional disorders and malignant brain tumors [5,54,60].

With the development of improved techniques of stereotaxis and cerebral angiography, the radiosurgical approach was applied to the treatment of arteriovenous malformations (AVMs) at MGH-HCL by Kjellberg et al [37] in 1965 using charged-particle beams and at the Karolinska Institute by Leksell et al [59] in 1968 using a multisource $^{60}$Co $\gamma$-ray unit (*gamma knife*). More recently, the advent of high-resolution computed X-ray tomography (CT) and magnetic resonance imaging (MRI) has made it possible for reliable stereotactic localization and irradiation techniques to be applied to the treatment of a diverse collection of intracranial disorders (Table 2). In the past few years, these advances in neurologic imaging have been accompanied by both technological advances and significant commercial interest in various radiosurgical systems and in computer software dedicated to radiosurgical treatment planning and dose delivery. During the past five years, especially, all these factors have contributed to the dramatic increase in the number of institutions world-wide with radiosurgery facilities.

Although more than 15,000 patients have been treated with stereotactic radiosurgery since the 1950s, the ultimate role of radiosurgery has yet to be clearly defined. Current clinical applications of radiosurgery can be considered in the following categories: func-

tional brain disorders, pituitary hormone suppression, pituitary adenomas, other benign intracranial tumors, vascular malformations, primary malignant brain tumors and brain metastases. Demonstration of long-term clinical efficacy thus far has been restricted primarily to the treatment of pituitary adenomas, acoustic neuromas and AVMs. Even for these conditions, however, the optimal treatment parameters have still not been clearly established, for example, as regards lesion size or location.

The expanded application of stereotactic radiosurgery is an important development in radiotherapy and neurosurgery, which promises new and innovative approaches that will influence therapeutic strategies, not only in the brain but elsewhere in the central nervous system and at other sites within the body. The objectives of this chapter are: (1) to describe the spectrum of human research studies thus far carried out in the development of clinical radiosurgery; (2) to discuss selected medical applications and the clinical experience and results; (3) to examine certain radiobiologic principles as they relate to focal brain irradiation; and (4) to suggest some potential future directions for the radiosurgical approach to influence and modify current therapeutic strategies. A comprehensive review of these topics is beyond the scope of this chapter. Selected historically significant or representative studies, therefore, have been summarized and/or cited for further reference.

## FUNCTIONAL RADIOSURGERY

Leksell's [56,58] original concept for stereotactic radiosurgery was motivated by the prospect of creating very small, well-defined regions of coagulative necrosis in deep fiber tracts or thalamic nuclei for functional ablation of various brain structures, while avoiding the potential risks of infection or intracerebral hemorrhage associated with corresponding invasive surgical procedures. Applications of functional radiosurgery thus far have included treatment for Parkinsonian tremor, intractable pain from cancer or trigeminal neuralgia, obsessive-compulsive neurosis and refractory epilepsy.

Radiosurgical thalamotomy (using Bragg-peak protons [48], Bragg-peak helium ions [53] and $^{60}$Co $\gamma$-rays [67]) for treatment of Parkinsonian tremor was used in limited numbers

of patients from the late 1950s to early 1970s with disappointing results. Recent anecdotal reports have suggested the possibility of a more favorable response with the use of modern stereotactic techniques of target definition and dose localization [67]. Thalamotomy has also been performed with the gamma knife by Steiner et al [106] for treatment of intractable cancer pain; *good* or *moderate* pain relief was reported in 26 of 52 patients treated, and doses of 160 to 180 Gy (using 3 x 5 mm or 3 x 7 mm beam collimators) were considered optimal. The development of improved pharmacologic therapy, however, has largely precluded the need for these functional radiosurgery procedures.

Forty-six patients with trigeminal neuralgia were treated with stereotactic radiosurgery of the Gasserian ganglion using the first prototype of the gamma knife; treatment volumes and doses were not specified [67]. Localization was accomplished using bony landmarks alone in 24 patients and by stereotactic cisternography in 22 patients. Of the latter 22 patients, 13 were pain-free after 6 months, but only four after 2.5 years.

A few patients have been treated for obsessive-compulsive and anxiety neurosis using gamma knife radiosurgery to sever frontolimbic connections (bilateral anterior capsulotomy) [101]. The lowest effective dose for production of MRI-detectable lesions was 160 Gy [93]. Long-term psychological effects have not yet been reported.

Recent advances in localization of epileptogenic foci have increased interest in the potential applications of stereotactic radiosurgery as an alternative to conventional surgery for eradication of refractory seizure foci [7,20]. Preliminary results are said to be encouraging [67]. Appropriate target volumes and doses, however, have not yet been defined.

Although the number of patients thus far treated with radiosurgery for various functional disorders has been relatively small, certain observations can be made: (1) the radiosurgical lesion should be as small as possible ($< 200$ mm$^3$) to minimize injury in adjacent tissues; (2) induction of these very small lesions requires relatively high doses ($\geq 160$ Gy) to induce coagulative necrosis reliably; (3) functional radiosurgery has generally not been as effective clinically as corresponding surgical procedures; and (4) recent advances in neurologic

imaging and stereotactic localization may lead to improved results.

## PITUITARY SUPPRESSION

Radiosurgical ablation of the pituitary gland can be considered as a special category of functional radiosurgery, in which reliable stereotactic localization of the target volume can be accomplished using plain radiographs of the sella turcica [61]. Pituitary radiosurgery has been shown to be very effective for inducing suppression of normal pituitary function with minimal associated risk of inducing injury in the adjacent neural structures [39,50,51,54,55, 61,63,78,92,100]. The range of acceptable doses for pituitary ablation has been established by clinical experience in more than 1,300 patients since 1954, and the latency interval to the onset of hypopituitarism has been shown to be inversely related to the treatment dose [61]. The primary applications of radiosurgical hypophysectomy have been to control the malignant spread of selected hormone-responsive carcinomas and to induce regression of proliferative diabetic retinopathy.

In North America, pituitary ablation treatment is no longer in common use. In the case of metastatic breast carcinoma, for example, modern anti-estrogenic drugs are now available for selective use guided, in part, by reliable estrogen-receptor classification of tumors. In the case of diabetic retinopathy, pituitary ablation treatment has also fallen out of favor. Nonetheless, the extensive clinical experience accrued has served to provide considerable information about radiation tolerance of the pituitary gland, parasellar tissues, cranial nerves and temporal lobes [100]. Although many of the early patients in the UCB-LBL series received total radiation doses that were divided into three to eight equal fractions, it should be noted that *each* dose fraction consisted of 20 to 50 Gy and that stereotactic localization and dose-delivery techniques were applied.

### Hormone-Dependent Metastatic Carcinoma

Between 1954 and 1972 at UCB-LBL, stereotactically-directed plateau beams of protons (initial 26 cases) or helium ions (157 cases) were used for pituitary-ablation treatment in

183 patients with metastatic breast carcinoma (an additional three patients were treated for metastatic prostate carcinoma) [16,50,54,61,114,115]. The pituitary gland was irradiated with total doses of 180 to 220 Gy (given in six to eight fractions over 2 to 3 weeks in the early years of the clinical program and in three or four fractions over 5 days thereafter); each fraction consisted of 30 to 50 Gy. Many patients experienced long-term remissions. Eight cases of focal radiation necrosis limited to the adjacent portion of the temporal lobe occurred; all were from an earlier group of patients who had received higher doses to suppress pituitary function as rapidly as possible [86]. Clinical manifestations of temporal lobe injury and transient cranial nerve involvement occurred in only four of these patients.

Minakova et al [78,92] have reported *excellent* results following stereotactic plateau-beam proton radiosurgery in Moscow in a series of 489 patients with metastatic breast carcinoma and in a series of 92 patients with metastatic prostate carcinoma (Ye. I. Minakova, personal communication). Konnov et al [44] have also reported *excellent* clinical results in patients treated with 120 to 180 Gy plateau-beam proton radiosurgery in St. Petersburg. In a series of 91 patients with bone metastases, 93% had relief of pain following treatment. Of 45 patients treated for metastatic disease with combined medical therapy and proton-beam hypophysectomy, 20 had no signs of recurrence or metastases after a follow-up period of 2 to 6 years. Kjellberg et al have used Bragg-peak proton-beam therapy of the pituitary to treat 31 patients with metastatic breast cancer at MGH-HCL (R. N. Kjellberg, personal communication).

## Diabetic Retinopathy

Between 1958 and 1969 at UCB-LBL, 169 patients with proliferative diabetic retinopathy received stereotactic plateau-beam helium-ion pituitary irradiation. This procedure was performed to evaluate the effect of pituitary hormonal suppression on proliferative diabetic retinopathy. Earlier reports had suggested that surgical hypophysectomy resulted in regression of proliferative retinopathy in many diabetic patients, a phenomenon believed related

to decreased insulin requirements and lowered growth hormone levels [80,81]. The first 30 patients in this cohort were treated with 160 to 320 Gy delivered in six to eight fractions (27 to 50 Gy per fraction) over 11 days to effect total pituitary ablation; the subsequent 139 patients underwent subtotal pituitary ablation with 80 to 150 Gy delivered over 11 days. Most patients had a 15% to 50% decrease in insulin requirements; this result occurred sooner in patients receiving higher doses, but ultimately both patient groups had comparable insulin requirements. Fasting growth hormone levels and reserves were lowered within several months after irradiation. Moderate to good vision was preserved in at least one eye in 59 of 114 patients at 5 years after pituitary irradiation (J.H. Lawrence, unpublished). Of 169 patients treated, 69 patients (41%) ultimately required thyroid replacement and 46 patients (27%) required adrenal hormone replacement. There were four deaths from complications of hypopituitarism. Focal temporal lobe injury was limited to an early group of patients that had received at least 230 Gy to effect rapid pituitary ablation in advanced disease; four patients in this high-dose group developed extraocular palsies. Neurologic injury was rare in those patients receiving doses less than 230 Gy (J.H. Lawrence, unpublished).

In a series of 25 patients treated with 100 to 120 Gy plateau-beam proton radiosurgery in Russia, Konnov et al [44] found that those with higher visual acuity and without proliferative changes in the fundus had stabilization and regression of retinopathy after treatment; microaneurysms were decreased and visual acuity was stabilized or improved. However, patients with poor visual acuity and progressive proliferative retinopathy responded less favorably. A reduction in insulin requirements was observed in all patients. Kjellberg et al [39] reported comparable results following stereotactic Bragg-peak proton radiosurgery in 183 patients.

## Histopathologic Studies

Histopathologic observations on autopsies from early patients, who had received helium-ion pituitary irradiation for hormonal suppression of metastatic breast carcinoma, confirmed

that more than 95% of pituitary cells were destroyed and replaced with connective tissue in a period of several months with doses of 180 to 220 Gy delivered in 2 or 3 weeks total time [86,118]. At lower doses, the magnitude of the histologic effects depended on the dose at the periphery of the pituitary gland, where viable hormone-secreting cells were usually found [61,113].

Woodruff et al [118] performed autopsies on 15 patients who had been treated with stereotactic plateau-beam helium-ion irradiation of the pituitary gland at UCB-LBL. Ten of these patients had been treated for progressive diabetic retinopathy with average doses of 116 Gy delivered in six fractions. All cases demonstrated progressive pituitary fibrosis. However, no radiation changes were found in the surrounding brain tissue or cranial nerves, demonstrating that plateau-beam radiosurgery applied with relatively high doses created a sharply-delineated pituitary lesion.

## PITUITARY ADENOMAS

Since 1958, more than 2,500 patients world-wide with pituitary adenomas have been treated with stereotactic irradiation of the pituitary gland as a primary noninvasive treatment, as adjunctive radiation therapy for incomplete operative resection and as treatment for late recurrences after surgery [4,6,19,38,61,68,83,90,111]. Radiosurgery has been applied to the treatment of acromegaly, Cushing's disease, Nelson's syndrome and prolactin-secreting tumors, as well as to the treatment of nonfunctioning and selected other adenomas. At UCB-LBL, helium-ion radiosurgery has resulted in reliable control of tumor growth and suppression of hypersecretion in a great majority of the 475 patients treated for pituitary adenomas [61]. Excellent clinical results have also been achieved with proton-beam Bragg-peak radiosurgery in nearly 1,100 patients at MGH-HCL [38,40], with plateau proton-beam radiosurgery in nearly 700 patients in Russia [44,83,90] and with gamma knife radiosurgery in about 300 patients [19]; smaller numbers of patients more recently have been treated with linear accelerator-based radiosurgical systems.

Prior to the introduction of transsphenoidal microsurgery, surgical hypophysectomy was often associated with high morbidity and mortality, and stereotactic radiosurgery was considered to be an excellent alternative treatment. With the development of safe and effective transsphenoidal techniques, the extensive clinical use of primary radiosurgical treatment, concentrated for many years in the Stockholm, Boston and Berkeley programs, has decreased significantly. Currently, primary radiosurgery for treatment of microadenomas is most often limited to patients who are considered to be poor surgical candidates or who have refused surgery. Proton-beam radiosurgery, however, remains as a primary therapeutic procedure for treatment of pituitary tumors in Russia [44,61,83,89,90]. The radiosurgical approach is now being applied mostly as adjunctive therapy in combination with microsurgery, where complete removal of large adenomas is not possible or for recurrences of tumor growth.

The therapeutic goals in the primary radiosurgical treatment of pituitary adenomas are control of tumor growth and hormonal hypersecretion, with acceptably low hormonal and neurologic complications. These goals have been met with remarkable success over the past 35 years, especially considering the limitations of the available neuroradiologic imaging methods during the early years of these investigations. The clinical and metabolic follow-up data describing the response of pituitary adenomas to radiosurgery have been reported extensively; the reader is referred to references [23] and [61] for more detailed reviews. In this section, the emphasis is limited to a brief discussion of dose considerations and selected clinical studies on acromegaly, Cushing's disease and complications of treatment.

## Dose Selection

In the pituitary irradiation program at UCB-LBL, plateau helium-ion beams were directed stereotactically in six to eight fractions over 2 to 3 weeks in the first few years of the program, and in three or four fractions over 5 days subsequently [113]. In Cushing's disease, maximum central doses to the pituitary gland ranged from 50 to 150 Gy, most often delivered in 3 or 4 daily fractions. The dose to adjacent cranial nerves and temporal lobes

was considered to be the limiting factor rather than the dose to the pituitary gland; the medial aspect of the temporal lobe was restricted to 36 Gy during longer courses of therapy and to 30 Gy during shorter courses of treatment. As the dose fell off rapidly from the central axis, the dose to the periphery of larger pituitary targets (e.g., acromegalic tumors) was considerably less than the peripheral dose to smaller targets (e.g., Cushing's disease).

Kjellberg et al [38] has empirically derived a method for selection of treatment dose for single-fraction Bragg-peak proton therapy according to the beam diameter used and the therapeutic objective for the particular diagnostic category (i.e., the desired degree of radiation necrosis). The highest dose range is used for acromegaly and Cushing's disease. Lower doses, but still within the "necrotizing range," are used for prolactin-secreting tumors and Nelson's syndrome. Subnecrotizing doses are considered sufficient for nonfunctioning adenomas. Within each category, larger-diameter beams are considered to require lower doses to produce biologically-equivalent responses. Selected adenomas with extrasellar extension are treated using a "beam-within-a-beam" technique; here, a subnecrotizing dose (e.g., 10 Gy) is given to the larger overall target volume, and an additional necrotizing dose (e.g., 35 Gy) is given to the smaller intraclinoid volume.

## Acromegaly

At UCB-LBL, stereotactic helium-ion plateau-beam radiosurgery has proven to be very effective for the treatment of acromegaly in 318 patients [49,52,68]. A sustained decrease in serum-growth hormone (GH) secretion was observed in most patients; the mean serum-GH level in a cohort of 234 of these patients decreased nearly 70% within 1 year and continued to decrease thereafter. Normal levels were sustained during more than 10 years of follow-up. Comparable long-term results were observed in a cohort of 65 patients who were irradiated with helium ions because of residual or recurrent metabolic abnormalities persisting after surgical hypophysectomy. Serial GH levels were examined before and after helium-ion irradiation as a function of neurosurgical grade. Statistically significant differences ($p <$

0.01) in fasting GH existed only between the microadenoma patients with normal sellar volumes (Hardy's Grade I [30]) and patients with macroadenomas (Grades II through IV) [68]. Grade I patients responded very well and have a good prognosis for cure; a lower incidence of post-treatment hypopituitarism was also observed in these patients. The more invasive tumors were slower to respond, but by 4 years after irradiation they were associated with GH levels not statistically different from levels found in patients with Grade I tumors.

Treatment failures following helium-ion irradiation generally resulted from failure to assess accurately the degree of extrasellar tumor extension [49,52,68]. Conversely, failure to identify the precise location and limit of intrasellar tumors necessitated that a larger-than-optimal portion of normal functional pituitary gland be included in the radiosurgical target; this difficulty has presumably resulted in an incidence of hypopituitarism in excess of what should now be attainable with the improved definition of pituitary tumors and adjacent neural tissues made possible by recent advances in MRI and CT scanning. These imaging considerations highlight the evolving role of stereotactic radiosurgery for the treatment of macroadenomas which extend into the cavernous sinus, sphenoid sinus or region of the optic chiasm [61,68].

Kjellberg et al [38,39,40] have now treated over 580 patients with acromegaly using Bragg-peak proton irradiation at MGH-HCL. Therapy has resulted in objective clinical improvement in about 90% of a cohort of 145 patients 24 months after irradiation. By this time, 60% of patients were in remission (GH level $\leq$ 10 ng/mL); after 48 months, 80% were in remission. About 10% of patients failed to enter remission or to improve, and they required additional treatment (usually transsphenoidal hypophysectomy).

### Cushing's disease

Cushing's disease has been treated successfully at UCB-LBL using stereotactic helium-ion plateau-beam irradiation [49,52]. In 83 patients (aged 17-78 years) thus far treated, mean basal cortisol levels in a cohort of 44 patients and dexamethasone-suppression testing

in a cohort of 35 patients returned to normal values within 1 year after treatment and remained normal during more than 10 years of follow-up [68]. All five teenage patients were cured by doses of 60 to 120 Gy without concomitant hypopituitarism or neurologic sequelae; however, nine of 59 older patients subsequently underwent bilateral adrenalectomy or surgical hypophysectomy due to relapse or failure to respond to treatment. Of the nine treatment failures, seven occurred in the earlier group of 22 patients treated with 60 to 150 Gy in six alternate-day fractions; when the same total doses were given in three or four daily fractions, 40 of 42 patients were successfully treated [68]. The marked improvement in response to reduced fractionation in the Cushing's disease group of patients has provided support for the single-fraction irradiation treatment of pituitary adenomas.

Kjellberg et al [38] have treated over 175 Cushing's disease patients with Bragg-peak proton-beam irradiation at MGH-HCL. Complete remission with restoration of normal clinical and laboratory findings has occurred in about 65% of a cohort of patients followed-up for 24 months; another 20% were improved to the extent that no further treatment was considered necessary.

Degerblad et al [19] reported long-term follow-up in a series of 35 patients with Cushing's disease treated with gamma knife radiosurgery (70 to 100 Gy, single dose). Urinary cortisol levels normalized in 76% of patients, about half of them within 1 year after irradiation and the rest within 3 years. However, most patients required more than one radiosurgical treatment to achieve normalization of adrenocorticotropic hormone levels. No recurrences were reported during follow-up lasting from 3 to 9 years. Delayed pituitary insufficiency developed in 55% of these patients.

## Complications

Following stereotactic helium-ion plateau-beam radiosurgery, variable degrees of hypopituitarism developed as sequelae of attempts at subtotal destruction of pituitary function in about one third of the patients, although endocrine deficiencies were rapidly corrected

in most cases with appropriate hormonal replacement therapy [68,100]. Diabetes insipidus has not been observed in any pituitary patient treated with helium-ion irradiation [68]. Other than hormonal insufficiency, complications in the pituitary tumor patients treated with helium-ion plateau radiosurgery were relatively few and limited most frequently to those patients who had received prior photon treatment. These sequelae included mild or transient extraocular nerve palsies, partial visual field deficits and seizures due to limited temporal lobe injury [68]. There were very few significant complications after the initial high-dose group of patients. After appropriate adjustments of dose schedules based on this early experience, focal temporal lobe necrosis and transient cranial nerve injury have been rare sequelae, in the range of 1% or less, and no other permanent therapeutic sequelae have occurred [68,86,100]. A very low incidence of significant adverse sequelae has also been reported in patients treated with Bragg-peak proton irradiation in the Harvard and Moscow experience and with plateau proton irradiation in the St. Petersburg series [38,44].

## OTHER BENIGN TUMORS

Stereotactic radiosurgery has been applied to the treatment of a variety of benign tumors, including acoustic neuromas [31,71,72,94,95,96], meningiomas [21,42,79] and craniopharyngiomas [3]. With benign tumors, a successful response to radiosurgery is generally defined not by complete radiologic disappearance of the tumor, but rather by lack of further tumor growth and/or improvement in symptoms. (With acoustic neuromas, preservation of hearing and other cranial nerve function are additional goals of treatment.) Radiosurgical treatment appears to inhibit tumor growth through cell death and necrosis with subsequent fibrotic replacement of tumor mass. Radiation-induced obliteration of the vascular supply to the tumor may also play a significant role in controlling or reversing tumor growth; this hypothesis has been supported by observations that loss of central CT-contrast enhancement is predictive of delayed tumor shrinkage in acoustic neuromas [71]. In general, clinical results have been excellent for acoustic neuromas and meningiomas, and particularly noteworthy for lesions that present substantial operative risk. Long-term follow-up evaluation

for some other categories of benign tumors has thus far been limited.

Norén et al [96] recently reported long-term outcome (mean follow-up, 54 months; range, 12 to 206 months) following 227 gamma knife procedures for treatment of acoustic neuroma. Initially, maximum central doses of 50 to 70 Gy were used, with peripheral doses of 25 to 35 Gy; doses were gradually reduced to 15 to 25 Gy centrally and 10 to 15 Gy peripherally. Based on CT and MRI evaluation, about 50% of tumors were decreased in size, 35% showed no change and 15% increased. Facial nerve weakness occurred in 16% of patients but was transient in all cases. Trigeminal dysfunction occurred in 20% of patients and persisted in about 8%. Hearing was unchanged in 22% of patients, slightly worse in 53%, much worse in 23% and improved in 2%. The clinical results were considered to compare favorably with the results for microsurgical resection. Linskey et al [71,72] reported comparable early results in a series of 101 patients.

Luchin et al [79] used proton-beam irradiation (two to four fractions; plateau-beam or Bragg-peak method) to treat 52 patients with cavernous sinus meningiomas. Maximum central doses of 50 to 70 Gy were used. With mean follow-up of 40.6 months (range, 13 to 77 months), local control was obtained in 84% of patients; five patients with inadequate dose-distribution in the tumor volume exhibited continued tumor growth.

Kondziolka et al [42] used gamma knife radiosurgery to treat 50 patients with meningiomas; the most frequent site of origin was the skull base. The actuarial 2-year tumor-control rate was 96%; only two patients have shown delayed tumor growth outside the radiosurgical treatment volume.

Comparison of radiosurgically-treated patients with surgically-treated and control groups is complicated by the variable natural history of these lesions. Meningiomas are generally well-circumscribed and slow-growing tumors, which may remain stable without treatment for many years. Untreated acoustic neuromas, on the other hand, occasionally remain stable, but more often they exhibit a wide range of potential growth rates [71]. The ultimate role of radiosurgery in the treatment of these benign tumors has yet to be defined, and long-

term clinical and radiologic follow-up will be required to assess the response to treatment and the incidence of delayed tumor regrowth.

## VASCULAR MALFORMATIONS

More than 3,000 patients world-wide since 1965 have been treated with stereotactic radiosurgery for vascular malformations of the brain (primarily, angiographically-demonstrable AVMs) [8,15,22,24,25,26,34,35,36,37,62,82,87,102,105]. The clinical objectives of radiosurgery for the treatment of AVMs are to achieve: (1) reduction or elimination of intracranial hemorrhage and its associated morbidity and mortality; (2) stabilization or reversal of progressive neurologic dysfunction; (3) lower frequency of seizures; and (4) fewer subjective complaints, including frequency and intensity of disabling headaches [24,62,102]. In order to achieve these objectives optimally, the entire AVM must be sclerosed and the local hemodynamic condition converted to normal or near-normal status. The mechanisms underlying the observed improvements in seizure activity and headache syndromes and the stabilization or improvement of progressive nonhemorrhagic neurologic dysfunction following radiosurgery are poorly understood. However, these changes appear to be associated, in large measure, with the improved regional cerebral blood flow, stabilization of hemodynamic imbalance and reversal of vascular steal associated with progressive thrombosis of the malformation [24,102].

As a result of extensive clinical experience, more is known about the efficacy of the radiosurgical procedure for the treatment of AVMs as regards patient selection criteria, treatment planning, dose prescriptions, clinical and neuroradiologic results and complications than for any other intracranial disorder. In general, the observed patterns of clinical response can be summarized as follows: (1) after a variable latency period, the likelihood of achieving complete AVM obliteration increases progressively over a period of about 3 years; (2) the probabilities of eventual AVM obliteration and adverse treatment sequelae both increase as the radiation dose increases; and (3) favorable response is achieved more readily with smaller lesions. The reader is referred to the original papers and reviews cited

at the beginning of this section for detailed information and analyses of these findings. Many uncertainties remain, however, regarding optimal radiosurgical treatment parameters for malformations of various sizes and locations in the brain [24,27,84,102] and the evolving role of embolization and/or microsurgery in combination with radiosurgery [85,104]. In this section, selected theoretical and practical issues are discussed, including the utility of radiosurgery for the treatment of angiographically-occult vascular malformations (AOVMs) [24,41,62,65,103] and carotid-cavernous fistulae [45].

## Mechanisms of Vascular Obliteration

Obliteration of AVM vasculature can be effected either by inducing a focal necrotic lesion encompassing the AVM or by inducing complete thrombosis of the AVM *without* significant parenchymal necrosis. Data from animal studies have suggested that the formation of focal tissue necrosis may be favored by somewhat higher doses (e.g., 30 to 50 Gy) and occurs with a shorter latency, whereas thrombotic obliteration of vascular structures without concomitant necrosis appears to be favored by somewhat lower doses (e.g., 15 to 25 Gy) and occurs with a longer latency [32,112,116]. The distinction between these two mechanisms of injury, however, is arbitrary and the transition between them most likely represents an overlapping and interdependent continuum [10]. Necrotizing doses appear to be very effective for the treatment of small AVMs in relatively silent regions of the brain; AVM obliteration can thereby be achieved relatively quickly and with minimal sequelae. However, similar doses may well be excessive for other more sensitive and eloquent brain regions or where larger volumes of normal tissue adjacent to the target volume are at risk. In these cases, lower (non-necrotizing) doses, associated with a more prolonged latency and/or lower cure rate, may be preferable. This consideration may have particular applicability to the treatment of large hemispheric AVMs and malformations in the brain stem and central nuclei [64].

## Dose–Volume Considerations

The rate and extent of AVM obliteration, as defined by angiographically-demonstrable change, and the incidence of adverse sequelae of treatment are dependent, in large measure, on treatment volume and dose [15,24,62,64,102]. Moreover, the response to dose is a threshold phenomenon; the minimum effective dose for obliteration of AVM shunts appears to be somewhere between 15 and 20 GyE [24]. Although dose reduction has lowered the incidence of delayed complications, it also may lead to undesirable clinical outcomes by decreasing the incidence of complete AVM obliteration or by extending the latency interval before complete obliteration occurs. By attempting to eliminate all potential risks of late complications, patients may be placed at increased risk of morbidity or mortality due to post-treatment hemorrhage.

The goal of complete AVM obliteration without adverse sequelae becomes progressively more difficult to achieve with increasing AVM size [24,100,102]. The volume of abnormal vasculature in a spherical AVM, for example, increases as the cube of the AVM radius, and the number of shunting vessels requiring thrombosis to ensure complete obliteration increases accordingly. From a radiobiologic perspective, the dose-response of a collection of vessels can be predicted by a Poisson distribution function [73]. For an equivalent dose, therefore, the probability of some vessels remaining patent after irradiation is greater for larger AVMs.

With increasing AVM size, the volume of normal tissue at risk for radiation injury also increases markedly. For the hypothetical spherical target volume, the differential volume at the AVM periphery increases as the square of the AVM radius. Since the dose-response relationship of this incremental normal tissue can also be presumed to follow a Poisson relationship, the risk of normal-tissue injury for any given dose increases with lesion size. This radiobiologic dilemma is further compounded because irradiation of larger target volumes is typically associated with shallower peripheral dose fall-off gradients, a phenomenon which further increases the volume of normal tissue at risk for radiation injury.

One promising strategy for the treatment of larger AVMs is to take advantage of the steeper peripheral dose gradients available with charged-particle radiosurgery as compared with photon-based radiosurgery [98]. Dose-volume histograms for charged-particle and photon-based radiosurgical systems have been shown to be fairly similar for irradiation of small target volumes, but to diverge very rapidly in favor of charged-particle radiosurgery for targets larger than 2 to 3 cm in diameter.

## A Role for Fractionated Stereotactic Irradiation?

In 1928, Cushing [17] described intraoperative findings in an AVM patient before and after radiation therapy. The initial surgical procedure was aborted due to excessive blood loss resulting from extreme friability of the large (5-cm diameter) AVM. Irradiation of the AVM was performed on an experimental basis to attempt to achieve sclerosis of the malformation; it was already well-known at that time that irradiation could induce sclerosis in cutaneous angiomas. The patient was given a total of 16 "deep X-ray" treatments (doses not specified) from January 1924 to February 1927. One month after the last treatment, a second craniotomy was performed because of the gradual development of renewed seizure activity and the onset of mild hemiparesis. The pulsatile vessels that had been seen initially were subsequently observed to be mostly thrombosed and transformed into "small bloodless shreds" that were easily separated from the adjacent normal cortex; the arterial intima had marked endothelial proliferation, often associated with complete vessel occlusion. These findings encouraged other investigators to conduct clinical trials using radiation therapy for the treatment of AVMs. The results with multifractionated irradiation in conventional doses, however, were disappointing and this approach was generally abandoned as unsuccessful [33,46]. When the AVM-irradiation technique was changed to stereotactic irradiation with high fractional doses (i.e., radiosurgery), on the other hand, considerable success was achieved.

In theory, the phenomenon of enhanced vascular-obliteration response to radiosurgery

(vis à vis conventional radiation therapy) might be explained by considering that, for an equivalent level of biologic effectiveness in tissue, a much higher total dose is required for conventionally-fractionated irradiation than for single-fraction irradiation [66]. Available data suggest that fractionated-irradiation protocols have not yet been evaluated at doses high enough to be biologically equivalent to effective single-fraction doses [46]. Higher doses of multifractionated irradiation very likely would lead to increased rates of AVM obliteration, although these higher total doses, if applied using broad-field techniques, would also be expected to lead to increased risks of normal-tissue injury [27]. Hypothetically, this problem would be minimized if comparably-fractionated high-dose treatments were delivered to the target volume using stereotactic irradiation techniques and dose distributions. This approach is currently under investigation for the treatment of selected malignant tumors [9,99]. It remains uncertain, however, whether this strategy would favorably or unfavorably alter the therapeutic ratio in the treatment of AVMs, where the target tissue consists of abnormal vascular shunts rather than neoplastic cells.

## Multistage Treatment

An increasing number of patients are now being evaluated for multistage procedures, including embolization and/or partial surgical resection in selected cases, to reduce malformation size and decrease the high rate of blood flow in preparation for radiosurgery. Although this approach is proving useful for certain large and complex malformations, the potential for serious additive complications has been recognized [24]. Consequently, these adjunctive procedures are currently indicated only under special circumstances, such as for cases where there is a high likelihood of achieving significant reduction in the radiosurgical target volume or where a limited number of large arteriovenous fistulae appear to be supplying major portions of the AVM.

An area of current research is the potential value of microsurgical resection and/or embolization *following* radiosurgery in selected cases with incomplete vascular response

[85,104]. Steinberg et al [104] have reported a series of eight patients who underwent complete microsurgical resection of their AVMs after incomplete obliteration following helium-ion radiosurgery. Most of these AVMs began as very large lesions (20 to 80 $cm^3$) located in or adjacent to eloquent brain regions and extending deep into the white matter. While follow-up angiograms 2 to 3 years after radiosurgery had shown little change in AVM volume, there appeared to be decreased flow within the AVM, thought to be associated with radiation-induced obliteration limited to the small-vessel component. Three of these patients underwent embolization of their AVMs before microsurgical resection. At surgery, all eight AVMs were found to be markedly less vascular and more easily resected than had been anticipated had they not undergone prior radiosurgery. Clinical outcomes were excellent in all eight patients. Stereotactic radiosurgery followed a few years later by open microsurgery appears to be a promising multistage-management approach for treatment of selected large and complex AVMs that have not responded fully to initial radiosurgical treatment.

## Incomplete Vascular Response

Patients with AVMs remain at some risk from hemorrhage until their AVMs are completely obliterated [102,105]. The data are too sparse at present to determine whether some degree of protection against hemorrhage is conferred during the prolonged latency period before complete obliteration occurs or by incomplete obliteration following irradiation with doses greater than some thus-far-undefined threshold. It has been suggested that microscopic thickening of AVM vessel walls, in the absence of complete AVM obliteration, may protect against hemorrhage or mitigate its severity [37]. However, if irradiation is restricted (e.g., by technical constraints) to a portion of an AVM ("partial-volume radiosurgery"), the potential benefit of vessel-wall thickening may be forfeited. Moreover, it has been hypothesized that incomplete AVM obliteration following partial-volume radiosurgery may be accompanied by an increase in outflow-resistance in the remaining vascular shunts, thereby predisposing the AVM compartment to hemorrhage before obliteration is complete [73].

## Angiographically-Occult Vascular Malformations

Stereotactic radiosurgery of AOVMs presents complex problems in diagnosis, patient selection criteria, treatment planning, dose selection and criteria for clinical and neuroradiologic follow-up evaluation [24,41,62,65,103]. It is recognized that slow-flow AOVMs comprise a number of pathologic conditions, and that only about half of clinically-symptomatic AOVMs are histologically similar to AVMs that are angiographically demonstrable [74]. Accordingly, mechanisms of radiation-mediated thrombotic vascular obliteration associated with AVM radiosurgery may not apply to many AOVMs. In the absence of established criteria for differentiating the various types of AOVMs, patients must be evaluated for radiosurgical treatment based on their clinical symptoms and neuroradiologic studies. Moreover, it is difficult to determine the appropriate radiosurgical target with certainty, and it may be necessary, therefore, to include some sensitive normal tissue within the target volume to ensure that the abnormal vasculature is enclosed by the target volume. Unfortunately, even a small rim of necrosis in the brain stem or central nuclei, e.g., may cause significant neurologic dysfunction. Furthermore, there is no radiologic standard by which to verify a successful response to treatment, because current imaging techniques are not sufficiently sensitive for imaging the obliterative response in AOVMs. Improvements in diagnostic specificity should provide improved criteria for patient selection for stereotactic radiosurgery and aid in image correlation for treatment planning and long-term evaluation of clinical and neuroradiologic response to treatment [61,62,65,102]. At present, it remains uncertain whether radiosurgical treatment of symptomatic inoperable AOVMs favorably alters their natural history.

## Carotid-Cavernous Fistulae

Stereotactic radiosurgery with plateau-beam proton irradiation has been used by Minakova and colleagues [45,88,89,91] to treat 24 patients with carotid-cavernous fistulae (Ye. I. Minakova, personal communication). Patients were treated with 40 to 60 Gy in

one or two fractions. Thus far, all patients have had regression of ocular symptoms and headaches, usually between 4 and 8 months after treatment. In four of eight patients examined, complete obliteration of the fistulae was observed on follow-up angiograms; three other patients had partial fistulae obliteration.

## PRIMARY MALIGNANT TUMORS

The role of radiosurgery in the treatment of primary malignant brain tumors is not well defined. While the hallmark of radiosurgery is a sharply-delineated dose-distribution delivered in a single or limited number of fractions, this approach would be expected to result in a less favorable response in malignant tumors than conventional large-field fractionated radiotherapy. Firstly, the property of sharp dose fall-off is of dubious benefit, given that the invasive tumor edge typically infiltrates to a varying extent beyond the margins of gross tumor and/or reactive edema suggested by neuroradiologic evaluation. As with any form of radiation therapy, a "geographic miss" or significant underdosage to a tumor-containing volume may negate the possibility of effective treatment.

Secondly, delivering the total dose with a limited-fraction irradiation technique negates the well-recognized radiobiologic advantages of fractionated radiotherapy for the treatment of malignant tumors [66]. Normal tissues interspersed within the target volume generally repair radiation injury more efficiently between fractions than do tumor cells. Fractionation also enhances tumor-cell killing by permitting interfraction reoxygenation of radioresistant hypoxic tumor cells and by allowing redistribution of tumor cells into more sensitive phases of the cell-division cycle. These phenomena all contribute to a favorable therapeutic ratio of tumor-cell killing to normal tissue injury.

Given the apparent comparative advantages of conventional radiotherapy for the treatment of malignant tumors, it would appear that radiosurgery is probably best suited for "boost" therapy in combination with standard radiotherapy and/or interstitial implantation of radioactive sources or for palliative treatment [47,75]. However, when the logarithmic nature of cell killing is considered, the radiation sterilization of the core of the tumor volume

is not as big a therapeutic advantage as it may seem at first glance; for example, killing 50% of tumor cells represents a gain equivalent to only about 2.5 to 3.0 Gy of a conventional multifractionated regimen [66,117]. Nevertheless, some patients appear to have responded well to primary radiosurgical treatment, although long-term data on duration of response are not yet available. Colombo et al [14] evaluated a series of patients with low-grade astrocytomas following radiosurgery. Serial contrast-enhanced CT scans demonstrated a pattern of progressive tumor enlargement over a period of 6 to 9 months with the concomitant development of a contrast-enhanced ring corresponding to the border of the original treatment volume; from this time until 12 to 24 months following treatment progressive shrinkage of the lesion was noted. This radiologic pattern was comparable to that described in patients treated with interstitial radioactive implants [97].

Sturm et al [107] treated a series of 29 patients with malignant gliomas with doses of 60 to 70 Gy in two fractions within 5 days, using a linear accelerator-based radiosurgical system. Survival rates were similar to that observed with conventional radiotherapy. However, one third of patients developed severe side effects, due to necrosis and edema, 1 to 3 months after treatment. It was concluded that conventional fractionation schedules were preferable to radiosurgery.

Some recent reports have described the use of multiply-fractionated stereotactic irradiation for the treatment of malignant brain tumors [9,99]. The theoretical considerations underlying this promising approach are discussed below (see Section on Future Directions).

## METASTATIC TUMORS

The application of stereotactic radiosurgery to the treatment of intracranial metastatic lesions, particularly those that have been resistant to conventional external-beam radiotherapy, is proving to be a valuable alternative to invasive surgical procedures or prolonged courses of conventional radiotherapy [47,76,77,107,108]. Radiosurgical treatment for metastases has generally been associated with low morbidity, improved quality of life and extended survival for several years in certain cases.

Sturm and colleagues [108] were among the first to report the radiosurgical treatment of solitary brain metastases of low radiosensitivity (e.g., hypernephroma, adenocarcinoma). Twelve patients who had not had prior conventional radiotherapy were treated with doses of about 20 to 30 Gy delivered to the 80% isodose surface at the CT-defined tumor margin, using a linear accelerator-based radiosurgical system. Of seven patients followed at least 3 months, two had a complete response by CT, and all improved clinically. Similar results were obtained in an expanded series of 27 patients followed-up 1 to 42 months (mean, 8.5 months) [107]. Although mean survival was not improved in comparison with conventional treatment methods, radiosurgery offered the advantages of high efficacy, low incidence of side effects and short hospitalization times.

Loeffler et al [76] treated 18 patients with 21 brain metastases, recurrent or persistent after prior conventional radiotherapy and/or surgery, with single radiosurgical doses of 9 to 25 Gy, using a linear accelerator-based radiosurgical system. The median dose of prior whole-brain radiotherapy (refused in one case) was 36 Gy (range, 30 to 49 Gy); three patients had received an additional 10 to 30 Gy boost of conventional radiotherapy to the tumor site. With median follow-up of 9 months (range, 1 to 39 months), all tumors were controlled in the radiation field; two patients had tumor recurrence in the immediate margin of the tumor volume and were subsequently treated with surgery and interstitial implantation of radioactive iodine. Complications were limited and transient.

As opposed to primary malignant brain tumors, brain metastases are often well-circumscribed radiologically and more or less spherical, rendering them ideal geometric targets for radiosurgery. Since the treatment volume is generally small and presumed to contain little or no functional brain tissue, the risk of normal-tissue injury is generally not thought to represent a significant problem [76]. However, metastatic tumors are capable of microscopically invading adjacent tissues outside the radiologically-defined target volume; late marginal recurrence remains a concern in cases treated with radiosurgery as primary management without adjunctive fractionated whole-brain irradiation. The primary role of

radiosurgery may ultimately prove to be boosting the main tumor volume in concert with multifractionated large-field irradiation [47,76]. Radiosurgery also appears to be a useful and relatively safe method for treatment of recurrent metastases in patients previously treated with conventional irradiation [47,76].

## MISCELLANEOUS DISORDERS

Several thousand patients in the United States and Europe have been treated for ocular melanoma using tightly-localized Bragg-peak irradiation with protons or helium ions (50 to 80 Gy) typically delivered in five fractions over 7 to 12 days [12,18,29,119]; this treatment procedure can be considered as a form of fractionated stereotactic irradiation. In these clinical series, local control exceeding 95% has been achieved in selected patient groups, but distant metastases occurred in about 20% of patients. A large proportion of treated eyes maintained useful vision; however, enucleation due to complications was required in 7% to 12% of patients. A number of centers have recently initiated clinical trials with fractionated irradiation of ocular tumors using photon-based radiosurgical systems [13]; long-term clinical results are not yet available.

The management of juxtaspinal and base-of-skull tumors (e.g., chordomas and chondrosarcomas) is a complex problem in neurosurgery and radiation oncology. Complete surgical resection is uncommon, and most patients require post-operative irradiation. The proximity of these tumors to the spinal cord or brain stem, however, limits the radiation dose that can be safely delivered to the tumor with conventional radiotherapy techniques. High-precision charged-particle radiotherapy delivered with conventional fractionation (60 to 75 GyE tumor dose, approximately 2 GyE per fraction) with protons [1,109] and helium ions [11] has been used with good success; a 5-year actuarial local control rate of 82% has been achieved [1]. Recently, single-fraction gamma radiosurgery (20 Gy marginal dose) has been used to treat six patients with small (< 30 mm diameter) chordomas and chondrosarcomas [43]; no patient has thus far exhibited growth of treated tumor.

The treatment of angiographically-demonstrable vascular malformations of the cervical spinal cord is a potentially-important new application of radiosurgery. This approach has recently been employed using Bragg-peak helium-ion beams delivered through a single posterior port (unpublished data). The patient underwent a dorsal laminectomy before irradiation to minimize tissue inhomogeneities in the beam path and to place radiographic clips at the margins of the AVM to guide stereotactic localization. Follow-up angiography 12 months after treatment (20 GyE; two fractions) showed partial obliteration of the lesion.

## FUTURE DIRECTIONS

Promising avenues for future research include: (1) enhanced three-dimensional target definition; (2) improved dose distributions for large or irregular target volumes; and (3) evaluation of the role of fractionated stereotactic irradiation.

### Target Definition

Accurate delineation of the radiosurgical target volume is one of the most important aspects of any radiosurgical procedure. However, determination of the true three-dimensional configuration of the target volume is difficult to achieve, even under ideal circumstances, such as occur with relatively spherical lesions [98]. Imaging data from CT and MRI scans are constrained by limitations of tomographic slice thickness and slice separation. Even with high-resolution cerebral angiography, the available anatomic detail is limited by the angiographic views selected; obliquely-oriented and/or irregularly-shaped lesions viewed in orthogonal projections may well suggest an apparent target volume that falsely includes a substantial volume of normal tissue [28]. Improved three-dimensional target definition can be expected from future advances in the resolution of CT and MRI scanning and perhaps from the development of *tomographic angiography*. Improvements in the resolution of *physiologic imaging* (e.g., positron emission tomography, phosphorus-based MRI techniques) may serve to supplement *anatomic imaging* information and help establish more effective guidelines for determination of appropriate margins for irradiation of malignant tumors.

## Dose Distribution

With the expected development of better target definition, the next challenge will be to improve three-dimensional dose distributions for large or irregularly-shaped lesions. Currently, photon-based radiosurgery of these lesions often requires using multiple overlapping isocenters to achieve an adequate marginal isodose contour; this approach, however, can result in substantial dose inhomogeneity (including *hot* and *cold* spots) within the target volume. For all radiosurgical modalities, increasingly sophisticated treatment-planning software is being developed to help maintain these dose inhomogeneities within acceptable limits while minimizing the dose to sensitive adjacent normal tissues. Software is also being developed to accommodate the application of variable multileaf collimators for continuous beam shaping during photon-arc irradiation. For charged-particle radiosurgery, beam-scanning techniques are currently under development to effect variable spreading of the Bragg ionization peak as the beam sweeps across the target volume [28].

## Fractionated Stereotactic Irradiation

The disorders currently being treated with stereotactic radiosurgery techniques represent a broad continuum of benign and malignant diseases, with a correspondingly broad range of therapeutic goals (Table 2). It follows that optimization of treatment for these various disorders will require a diverse spectrum of radiobiologic strategies, of which fractionated stereotactic irradiation is among the most promising. With the development of stereotactic immobilization systems capable of reliable serial repositioning, this approach offers the potential for improved treatment outcome by combining the excellent dose-localization and dose-distribution characteristics of stereotactic radiosurgery with the favorable radiobiologic properties of fractionated irradiation [66]. Dividing the radiation dose into multiple fractions is well known to result in preferential killing of *early-responding* neoplastic cells vis à vis *late-responding* normal brain cells, i.e., a favorable therapeutic ratio [66].

Since the use of stereotactic irradiation makes it possible to reduce substantially the amount of normal tissue irradiated to relatively high doses for a given dose to the tumor (in a manner analogous to that achieved with brachytherapy), it also offers the possibility of improving the local tumor-control rate by increasing the tumor dose to significantly higher levels than those currently used in conventional irradiation, while still preserving acceptable normal-tissue tolerance and maintaining an adequate tumor margin. It remains to be determined whether this method will eventually replace brachytherapy in the treatment of primary malignant tumors.

These same considerations may also apply to the treatment of selected benign and metastatic brain tumors, and especially for lesions in particularly sensitive regions. There is compelling evidence that single-fraction radiosurgery is very effective for halting the growth of most benign tumors, but radiosurgery can be associated with a significant incidence of normal-tissue injury. For example, about 75% of acoustic-neuroma patients treated with radiosurgery experience hearing loss, and a small number have trigeminal nerve dysfunction. One hypothesis to consider is whether fractionated stereotactic irradiation can reduce the incidence of cranial nerve dysfunction while maintaining equivalent rates of tumor control. On the other hand, multiply-fractionated stereotactic irradiation may be less likely to alter the therapeutic ratio favorably when the abnormal target tissues are late-responding vascular endothelial cells (e.g., AVMs) rather than early-responding neoplastic cells [66].

## CONCLUSIONS

Stereotactic radiosurgery has been the subject of extensive basic and clinical research for four decades. During this time, more than 15,000 patients world-wide have been treated using radiosurgical methods. In recent years, radiosurgery has been applied to an increasingly diverse collection of intracranial disorders. Clinical efficacy and relative safety have been well demonstrated for selected benign tumors and vascular malformations. For many other conditions, however, demonstration of clinical efficacy has yet to be firmly established, and optimal treatment parameters have yet to be determined. Fractionated stereotactic irradi-

ation is one of the most promising approaches for improved treatment outcome in patients with malignant brain tumors or lesions in radiosensitive regions.

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**Table 1**

**Characteristics of External-Beam Radiosurgery and Conventional Radiotherapy**

| Characteristic | Radiosurgery | Radiotherapy |
|---|---|---|
| Number of Fractions | one or a few | 12 to 35 |
| Duration of Course of Treatment | minutes to a few days | 3 to 7 weeks |
| Size of Treatment Fields | small (usually less than 5 cm diameter) | large (usually greater than 5 cm diameter) |
| Volume of Tissue Treated | small (usually less than 25 $cm^3$) | large (usually much more than 50 $cm^3$) |
| Location of Lesion | primarily intracranial | anywhere in body |
| Dose per fraction | about 15 to 50 Gy | about 1.8 to 2 Gy |
| Stereotaxis | yes | no |
| Entry Angles | many | few |
| Treatment Ports / Arcs | many | few |
| Purpose | alter structure and/or function of a cell population | destroy reproductive capacity of tumor cells |

## Table 2
## Reported Applications of Stereotactic Radiosurgery

**Functional Disorders**
Parkinsonian tremor
Intractable cancer pain
Trigeminal neuralgia
Obsessive-compulsive neurosis
Refractory epilepsy

**Pituitary Suppression**
Metastatic breast carcinoma
Proliferative diabetic retinopathy
Endocrine ophthalmopathy
Adrenogenital syndrome

**Pituitary Adenomas**
Acromegaly
Cushing's disease
Nelson's syndrome
Prolactin-secreting tumors
*TSH-secreting tumors
Nonfunctioning adenomas

**Other Benign Tumors**
Acoustic neuroma
Meningioma
Craniopharyngioma
Hemangioblastoma
Fifth nerve neuroma
Glomus jugular

**Vascular Malformations**
Angiographically-demonstrable
Angiographically-occult
- cavernous angioma
- capillary telangectasia
- venous angioma

Carotid-cavernous fistula
Arterial aneurysms

**Primary Malignant Tumors**
Astrocytoma, anaplastic
Astrocytoma, low-grade
Glioblastoma multiforme
Oligodendroglioma
Pineal tumors
Ependymoma
Germinoma
Medulloblastoma
Lymphoma

**Metastatic Tumors**

**Miscellaneous Disorders**
Ocular melanoma
Chordoma
Chondrosarcoma
Spinal vascular malformations

* TSH = thyroid stimulating hormone

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