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REVIEW ARTICLE

Photon Radiosurgery: A Clinical Review

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ABSTRACT: The term radiosurgery has been used to describe a variety of radiotherapy techniques which deliver high doses of radiation to small, stereotactically defined intracranial targets in such a way that the dose fall-off outside the targeted volume is very sharp. Proton, charged particle, gamma unit, and linear accelerator-based techniques appear to be equivalent from the standpoint of accuracy, dose distributions, and clinical results. However, capital and operating costs associated with the use of linear accelerators in general clinical use are much lower. Radiosurgery has an established role in the treatment of arteriovenous malformations and acoustic neurinomas. Interest in these techniques is increasing in neurosurgical and radiation oncological communities, as radiosurgery is rapidly assuming a place in the management of several other conditions, including craniopharyngiomas, meningiomas, and selected malignant lesions.

RÉSUMÉ: Photoradiochirurgie: revue clinique. Le terme photoradiochirurgie est souvent utilisé pour décrire une variété de techniques en radiothérapie pour livrer une dose élevée de radiations à un petit volume cible intracrânien, défini par stéréotaxie, de sorte que le gradient de dose, en dehors du volume cible, s'abaisse brusquement. Les techniques basées sur l'utilisation de protons, de particules chargées, d'unités gamma et d'accélérateurs linéaires semblent équivalentes au niveau de la précision de distribution de la dose et des résultats cliniques. Cependant, le capital et les coûts d'opération reliés à l'utilisation d'accélérateurs linéaires en clinique générale sont bien moindres. La radiochirurgie a un rôle établi dans le traitement des malformations artérioveineuses et des neurinomes acoustiques. L'intérêt pour ces techniques est croissant en neurochirurgie et radio-oncologie, étant donné que las radiochirurgie prend de l'ampleur dans le traitement de plusieurs autres pathologies, incluant les crâniopharyngiomes, les méningiomes et certaines lésions malignes.

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Radiotherapy plays an important part in the management of many intracranial lesions. However, with conventional external beam irradiation, the ability to control many such lesions may be limited by the dose which may be administered, which, in turn, is limited by the tolerance of the volume of normal tissue that is also irradiated. The term 'radiosurgery' has been used to describe a variety of radiotherapy techniques, which may overcome these limitations by the accurate delivery of high doses of radiation to stereotactically defined intracranial targets in such a way that the dose fall-off outside the targeted volume is very sharp. These techniques have already been established to be of value in the treatment of a number of malignant and non-malignant conditions, the best known being arteriovenous malformations. Interest in their future role in the treatment of these and other lesions is growing in neurosurgical and radiation oncological communities alike.

HISTORICAL DEVELOPMENT OF RADIOSURGERY

The development of stereotaxy to localize intracranial structures in three dimensions dates back to the use of a guiding device first used in neurophysiological experiments in animals in 1873.[1] In 1889, Zernoff[2] used his 'Encephalometer' in human surgery, although, more recently, it has been recognized that it was used in defining surface topography in the localization of cranial sutures and cerebral sulci.[3] In 1918, Mussen designed the first true stereotactic instrument for use in humans, although it was not actually used in surgery until the 1940's;[4] he evidently foresaw the use of his frame to localize an intracranial tumor, and to treat it with electrotherapy. It is not clear when stereotactic localization was first used with external beam radiotherapy in the treatment of intracranial lesions. Larson et al.[5] stated that stereotactic irradiation using orthovoltage apparatus and plaster of Paris headcast immobilization was administered at the University of California at San Francisco in 1945.

In 1949, Lars Leksell,[6] a neurosurgeon at the Karolinska Hospital in Stockholm, built a stereotactic instrument for open operations. Subsequently, he modified his device such that it could admit the collimator of an orthovoltage radiotherapy unit and multiple beams of radiation could be delivered at points distributed over the convexity of the skull.[7] The technique, which

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Leksell dubbed 'radiosurgery' was used initially to treat a variety of functional disorders. However, its use was discontinued because orthovoltage x-rays were not penetrating enough to give a sharp dose fall-off outside the targeted volume. Later, Leksell et al.[8] reported the use of high energy protons in the radiosurgical treatment of several patients, and that the use of the synchocyclotron that produced the proton beam was found to be clumsy. In 1968, Leksell first reported the use of a device in which multiple cobalt sources were used stereotactically to deliver multiple convergent photon beams; he called this a 'gamma knife'.[9] In subsequent years, he and other investigators from the Karolinska Hospital were to report on their pioneering work in radiosurgery.[7-21]

In the 1950's, the first patients were treated with protons at Boston[22] and Berkeley,[23] and, more recently, heavy charged particles at Berkeley.[24] However, it was not until the 1980's that other centers, outside Sweden, developed radiosurgery programs based on the gamma unit.[25,26] In addition, other techniques which employed apparatus in general clinical use, including conventional cobalt units,[27] linear accelerator (linac) units,[28-34] and neutron generators[35] have evolved. As interest in all of these techniques has increased, so also has the number of patients treated, and the number of centers in North America capable of administering radiosurgery. It has been estimated that, within a few years, there may be at least 6 gamma unit and 59 linac-based radiosurgery facilities in the United States.[36]

PRINCIPLES OF RADIOSURGERY

The aim of any radiosurgical technique is to deliver a high dose of radiation to a small, stereotactically localized volume, usually less than 40 mm in diameter, without delivering a clinically significant dose to adjacent normal tissues. Precision, the small volumes that are treated, high dose gradients at the field edges, and the fact that usually single fractions of irradiation are used, all distinguish radiosurgery from conventional external beam radiotherapy.[37] Podgorsak et al.[38] have summarized the main requirements for radiosurgical procedures, as follows: accurate determination of the target volume (within ± 1 mm) with stereotactic techniques; accurate knowledge of the dose required for treatment of a particular disease; very sharp dose fall-off in regions immediately outside the target volume; calculation of three-dimensional dose distributions, to determine distributions within and outside the targeted volume; accurate spatial (within ± 1 mm) and numerical (within ± 5%) delivery of dose to the pre-determined target volume; treatment accomplished in a reasonable amount of time; low skin dose (to avoid epilation) and low lens dose (to avoid cataract formation); and low or negligible scatter and leakage dose to radiosensitive organs (to avoid the somatic and genetic effects of radiation).

Following the application of a stereotactic frame to the patient's skull, imaging procedures — angiography, computerized tomography (CT), or magnetic resonance imaging (MRI) — are done to define the radiosurgery target volume within the coordinate system of the frame. A known fixed relationship between the treatment unit and the resulting coordinates allows accurate administration of radiation to the targeted volume. Details of this procedure are beyond the scope of this review, and the interested reader is referred to a previously published description.[39]

The accuracy of stereotactic localization with modern imaging techniques has greatly improved. For digital subtraction angiography (DSA), it has been shown that it may be within ±1 mm for all three coordinates.[39] For CT and MR imaging, accuracy may be within ± 1 mm for in-plane coordinates, and ± (slice thickness/2) for out of plane coordinates.[39] Positron emission tomography (PET) has been reported to have been used in stereotactic localization,[40] but its role has not been established definitively.

Stereotactic frames which are compatible with all imaging modalities are now commercially available. The use in the frame of low atomic number materials, such as aluminum or plastics, minimizes interference with the diagnostic CT beam, and the use of non-ferrous materials and design to avoid closed current loops is essential for compatibility with MRI.

Following stereotactic target localization, three dimensional (3-D) treatment planning must be undertaken in an effort to optimize radiation dose distribution with respect to the lesion to be treated, and to adjacent normal structures. Centers in which radiosurgery was administered in the past had to develop their own planning systems which display a three dimensional isodose distribution. Examples of such distributions may be found in Figure 1. More recently, 3-D planning systems have become available commercially. Limitations to many of these include

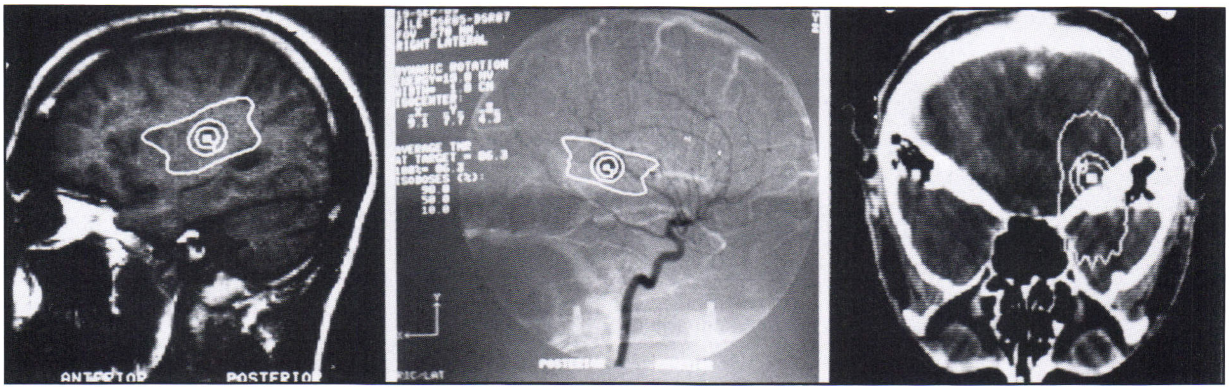

Figure 1 — Examples of dose distributions (90, 50, and 10% isodose lines) for the linac-based dynamic rotational technique displayed in the sagittal planes of magnetic resonance imaging and digital subtraction angiography, and the transverse plane of computerized tomography.

the fact that they are not very user friendly, and, importantly, that they do not display isodose contours directly superimposed upon the localization imaging of the patient. Moreover, commercial systems are relatively expensive, despite their drawbacks.

Radiosurgical Approaches

A number of radiosurgical approaches is currently employed in centers around the world. The use of protons, helium ions, and other charged particles have been shown to be of benefit in treated patients.[23,41] However, applicability of such therapy has been limited by the high cost and the considerable physics and technical support required in the development and maintenance of the cyclotrons which produce the treatment beam. Proton and charged particle therapy possesses theoretical advantages in treatment, relating to potentially very precise Bragg peak deposition of radiation energy. Cyclotrons treat patients with protons at the Massachusetts General Hospital, and with protons and other charged particles at the Lawrence Berkeley Laboratory.

The gamma unit is commercially available, and has been extensively tested and used to treat many patients in Stockholm,[19] and, more recently, in Pittsburgh[25] and Sheffield.[26] Several prototypes of the unit have been developed. In units in current use, 201 cobalt-60 sources converge upon a common focal point; each source is individually collimated with the use of one of four collimator helmets. Advantages to the use of the gamma unit include a high degree of precision in delivery of dose to the target to within a fraction of a millimeter, due to the lack of moving parts within the machine. Disadvantages to its use include a high initial capital cost, and the high cost of replacement of the cobalt sources, which is necessary every 4 to 6 years, and the fact that the unit may be used only for radiosurgery. A potential disadvantage may be the maximum final aperture size (18 mm) which necessitates the use of more than one target center in the treatment of larger lesions.

The costs of both charged particle and gamma unit-based radiosurgery and excellent treatment results reported in centers employing these units have spawned less expensive techniques based on linear accelerators which are widely available and in general clinical use in conventional radiotherapy.

These techniques have required modifications of the treatment couch, gantry, and collimation system. which may be made relatively inexpensively. Several commercial systems are now offered by the manufacturers of linear accelerators to render their units capable of administering adequate radiosurgery; these systems tend to be more expensive than in-house modifications.

Linear Accelerator-Based Radiosurgery

Current interest in the role of radiosurgery in the treatment of some intracranial conditions, and the high cost of other systems, promise that the number of linac-based radiosurgery facilities will increase markedly in the 1990's. Units that are already in existence have evolved separately and differently. In his review of the technical and physical aspects of linac radiosurgery, Podgorsak[42] has summarized the full range of additions and modifications that are made properly to adapt medical linear accelerators to use in radiosurgery.

Concern has been expressed that linear accelerators in general clinical use may not fulfill the stringent requirements for mechanical precision in radiosurgery.[21] Podgorsak[42] has reviewed the issue of accuracy in linac-based radiosurgery. For conventional external beam radiotherapy, the International Commission on Radiation Units and Measurements[43] has recommended an overall accuracy in dose delivery of ± 5% which also applies in radiosurgery. Spatial accuracy, which is the accuracy in the delivery of radiation to the prescribed targeted volume, is governed by the accuracy of target localization, localization of the isocenter, and positioning the target into the isocenter. With great care and attention to detail in treatment planning and patient setup, and diligent calibration and maintenance of equipment, the overall spatial accuracy of dose delivery is estimated to be ± 2 mm. Therefore, it can reasonably be said that linac-based radiosurgery may be administered with accuracy which is clinically very similar to that of other radiosurgery techniques.

Linac-based radiosurgical techniques are currently divided into four categories: a) the single plane rotation;[44] b) multiple non-coplanar converging arcs;[28,29,31,33] c) the dynamic rotation;[34] and d) the conical rotation.[45] Figure 2 illustrates the patient setup for radiosurgery using a linear accelerator at McGill University. Each is characterized by a particular patient position, and set of individual linac gantry and/or patient rotational motions from given start to stop angles. Linac-based techniques are summarized in Table 1.

Comparison of Radiosurgery Techniques

In a comparison of photon and proton radiosurgical techniques,[46] dose-volume histograms suggest that dose distributions are superior for protons. However, while this effect was much more marked with increases in the diameter of the high dose volume, when treating spheres less than 30 mm in diameter, histograms were comparable. Thus, in most clinical situations in which radiosurgical techniques may be used, photon and proton-based techniques are comparable.

A comparison of photon-based radiosurgical techniques has also recently been made, evaluating the steepness of the dose gradient at the edge of the target volume.[38,42] The energy of the treating photon beam does not appear to be important. With

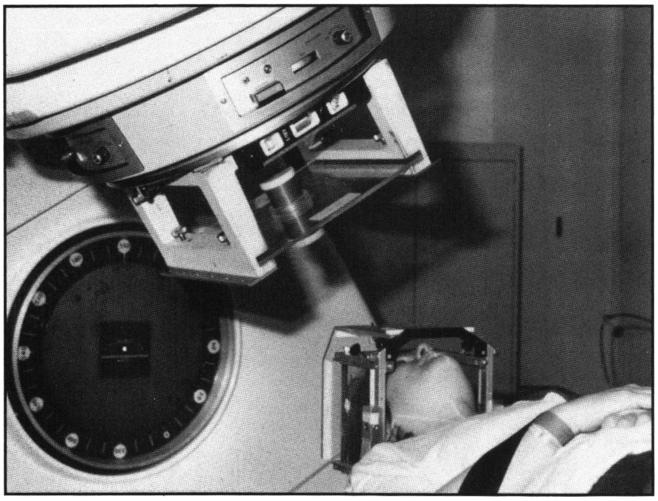

Figure 2 — Patient setup for the linac-based dynamic rotational technique at McGill University.

Table 1: Linac-Based Radiosurgical Techniques

Radiosurgical Technique	Institution	Patient Position
Single plane rotation[44]	U. of Miami Miami	supine on treatment couch
Non-coplanar converging arcs[28]	Hospital Español Buenos Aires	sitting on treatment chair
Non-coplanar converging arcs[29]	City Hospital Vicenza	supine on treatment couch
Non-coplanar converging arcs[31]	DKFZ Heidelberg	supine on treatment couch
Non-coplanar converging arcs[32]	Royal Hospital Wolverhampton	supine on treatment couch
Non-coplanar converging arcs[33]	Joint Center Boston	supine on treatment couch
Dynamic rotation[34]	McGill University Montréal	supine on treatment couch
Conical rotation[45]	Emory Clinic Atlanta	sitting on treatment chair

respect to technique, for the single plane rotation, dose fall off in a transverse plane compares poorly with that of the gamma unit, suggesting that this represents a poor alternative. Conversely, non-coplanar arc, conical rotation, and dynamic rotation techniques all compare quite favourably to the gamma unit, and to the theoretical ideal 2π distribution, in which an infinite number of photon beams is distributed over a hemisphere, the upper half of the skull. Another practical aspect in the consideration of linac-based radiosurgery techniques, particularly for a busy radiotherapy department, is relative ease and speed of treatment; the dynamic rotation technique may offer an advantage in this regard.

SPECIAL CONSIDERATIONS IN RADIOSURGERY

Dose Prescription

Comparisons between centers with respect to treatment technique and results are hampered by differing dose prescription conventions. Gamma unit treatments are usually prescribed to the 50% isodose surface. Centers that employ other units may prescribe to the 70, 80, or, commonly, to the 90% isodose surfaces. Advantages to prescribing to the last of these are increased dose homogeneity within the treatment volume, the more spherical shape of the 90% isodose surface, and shorter treatment times. It is hoped that the reporting of specific dose prescription information along with treatment results may facilitate their interpretation, although the exact clinical significance of such differences is not known.

Irregular Target Volumes

For the above radiosurgical techniques, high dose volumes are essentially spherical. Conversely most intracranial lesions are of an irregular shape. However, since lesions treated with radiosurgery are almost always small, one might argue that treating even the most elongated shape with a spherical volume would include only small volumes of normal tissue, and therefore be acceptable. Many centers attempt to tailor the high dose volume by using more than one isocenter, particularly in the use of the gamma unit.[47] Such attempts may make treatment planning complicated, produce large dose inhomogeneities, and increase the total treatment time. Flickinger et al.[48] describe shaping of isodose surfaces through the preplanned closure of some of the collimators in the gamma unit; however, this does not shape isodose surfaces above the 50%. Other techniques to shape isodose surfaces have not yet been applied clinically. It is not clear whether the increase in complication in planning and treatment with any of these techniques will be offset by improvement in clinical results, specifically in terms of reduced complication rates.

Surface and Scattered Dose with Radiosurgery

All radiosurgical techniques produce surface doses less than 1%, so that epilation is unlikely, although in the uncommon situation that a lesion which is quite superficial is treated, epilation may be a consideration.[42] If the lens is within a treatment beam, the dose it may receive is higher, approximately 2.5%, which nevertheless is below the threshold for cataractogenesis. Scattered doses to radiation sensitive organs are similar for the gamma unit[26] and linac-based radiosurgery,[49] amounting to 0.2%, 0.06%, and 0.02% of the isocenter dose to the thyroid, breast, and gonads, respectively. At these doses, the risk of radiation carcinogenesis is small, compared to the risk of morbidity from the lesion to be treated.

Fractionated Treatment

As noted above, the term "radiosurgery" most often refers to high doses of radiation delivered to a small stereotactically defined volume in a single treatment.[21] However, some centers are now applying the same techniques to deliver treatment in several fractions.[50-53] The rationale for this includes that the larger volumes of normal tissue that may be included in the treatment of malignant and some other lesions may tolerate fractionated therapy more readily than a single fraction, and that other radiobiological considerations, including cycling and reoxygenation of malignant cells, may be important. Consequently, fractionated treatment may improve the therapeutic ratio in some clinical situations. Only a few reports of small numbers of patients treated in this manner have been published. Although it has been shown to be possible from a logistical standpoint, it remains to be seen if it will prove to be advantageous clinically. There is some question whether fractionated treatments should ever be called "radiosurgery".[54] Despite this, it is likely that more reports of patients treated with irradiation administered with stereotactic techniques and delivered in several fractions, will be published in the near future.

CLINICAL APPLICATIONS OF RADIOSURGERY

In its early use at the Karolinska Hospital in the 1950's and 1960's, radiosurgery was applied primarily in the treatment of functional diseases. Doses as high as 250 Gy were administered to very small volumes localized by brain mapping for intractable pain, anxiety states, Parkinsonism, trigeminal neuralgia, and epilepsy.[9,10] With the advent of other treatment modalities for many of these disorders, and CT scanning, radiosurgery much more often has come to be used in the treatment of nonfunctional disease. In many instances, the number of patients that has been treated is small, so that definitive conclusions about the role of radiosurgery may not be drawn. However, radiosurgery has already become an integral part of the management of several clinical situations.

Arteriovenous Malformations (AVM's)

The yearly risk of first hemorrhage is approximately 1 to 4% per year,[55] and, for rebleed, as high as 6% in the first year.[56] One author found an overall lifetime risk of death of 29%.[56] AVM's are therefore clearly a potential cause of serious morbidity and mortality. Although surgery, with embolization as a possible adjunct, remains the treatment of choice for peripheral lesions, radiation therapy has become a treatment option for AVM's in inaccessible regions of the brain. The results of treatment with conventional, fractionated external beam radiotherapy have been unsatisfactory.[57] Radiosurgery has been established as the treatment of choice for inoperable arteriovenous malformations.

The exact mechanism of the effect of irradiation has not been fully defined. Kjellberg et al.[58] examined histopathological changes in patients who had received proton therapy for AVM's. These included occlusion of blood vessel lumina, with replacement of endothelium, medial cells, and elastic lamina by collagen, and marked thickening of blood vessel walls. Similar changes have been reported by other authors.[59] An associated vascular thrombosis[59,60] and surrounding intense gliosis[61] have also been seen.

The clinical experience of institutions treating AVM's establishes that the angiographic response to radiosurgery is slow, usually occurring over the 1 to 2 years following treatment, although some patients may eventually respond fully only after a 3 to 5 year period. Data from the Karolinska Hospital[19] suggest that, in the 1 to 2 year "latent" period during which obliteration of an AVM is occurring, there is no protection from further bleeding, and that, ultimately, no protection is conferred unless complete obliteration occurs. Steiner[19] reports that in patients with angiographically determined complete obliteration, mortality from recurrent hemorrhage has been only 0.2% overall. In all of his patients, Kjellberg[62] found rebleeding rates at 2 years or more following treatment which were lower in comparison with pre-treatment rebleeding rates, regardless of whether or not a complete obliteration had occurred.

The probability of complete obliteration appears to be influenced by the size of the AVM. Marks et al.[24] and Colombo et al.[59] both have found that complete response was less likely in larger AVM's. Thus far, there is no demonstrable relationship between prescribed dose and rate of complete angiographic response.[63] In contrast, Steiner[18] and Souhami et al.[64] have reported that inclusion of the entire nidus of an AVM within the volume that receives a significant dose — greater that 20 to 50 Gy — appears to optimize the rate of complete obliteration. Levy et al.[65] have reported similar findings in patients treated with helium ions. Reported results of helium ion,[65] gamma unit,[66,67] and linac-based radiosurgery[28,59,33,64] suggest that, at 1

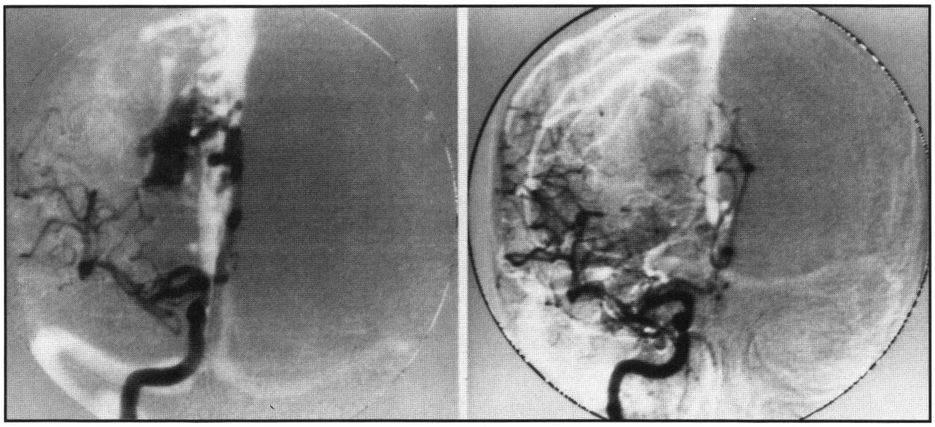

Figure 3 — Cerebral digital subtraction angiography in patient with a right parietal arteriovenous malformation, before and 13 months following radiosurgery, showing complete obliteration post-treatment.

year, angiographic complete obliteration will be seen in approximately 40% of patients; the complete obliteration rate at 2 years will be approximately 80%. The 2 year obliteration rate at the proton facility at the Massachusetts General Hospital[62] has been substantially lower, at 22%; this likely stems from the fact that the AVM's that were treated were substantially larger than those reportedly treated with other radiosurgical techniques.

In general, such excellent treatment results appear to be entirely independent of radiosurgical apparatus or technique employed. Further follow-up will be necessary to confirm that radiosurgery may reduce the frequency or seizures associated with an AVM,[67] the degree to which both angiographic complete and partial obliteration confer protection from later hemorrhage, and the influence of other patient and treatment factors on response rates and eventual clinical results. In the meantime, radiosurgery remains an important part of the range of therapies available for AVM's. DSA before and 13 months following linac-based radiosurgery in a patient with an AVM may be found in Figure 3.

Cavernous Angiomas

Small numbers of patients with angiographically occult vascular malformations (cavernous angiomata) have been treated.[68-70] Although there is little information in the literature on the natural history of these lesions, and little experience in managing them with radiosurgery, there are already some questions as to whether the results of treatment are as good as those of the treatment of classical AVM's. Weil et al. treated 6 patients, all of whom were followed for 2 years or more.[69] Followup imaging revealed no change in the size of any of the lesions; 2 of the patients had recurrent hemorrhage and 3 of them had apparent radiation-related complications. Ten patients with angiographically occult malformations have been treated with radiosurgery at McGill University. Although there was symptomatic improvement in 6 patients, there was reduction in the size of the lesion on MR imaging in only 2 patients. One of the 10 patients rebled and died at 33 months following radiosurgery; another patient rebled at 23 months following radiosurgery, and survived. In contrast, Kondziolka et al. treated 24 patients, all of whom had had previous hemorrhage.[70] One patient had recurrent bleeding and 4 patients developed apparent perilesional edema following radiosurgical treatment. There was subsequent reduction in the size of the lesion on followup MR imaging in 3 of 11 patients followed for 1 year or more. Further experience in the natural history and the results of radiosurgical treatment of these lesions is necessary to determine the optimum approach in their management.

Acoustic Neurinomas

Acoustic neurinomas may be causes of considerable morbidity, including hearing loss, balance difficulties, trigeminal or facial nerve palsies, or compression of the brain stem. In medically operable patients, classical management has included surgical excision, with conventional external beam radiotherapy occasionally being administered for patients with residual,[71] recurrent, or otherwise inoperable disease. Patients that are difficult to manage surgically include those with bilateral tumors and those with tumor on the side of the only hearing ear. This, in addition to a significant risk of morbidity from surgery,[72] including a high incidence of complete hearing loss, has led to the development of relatively non-invasive radiosurgical techniques.

Both the Stockholm[15,16] and Pittsburgh[73] gamma units have treated substantial numbers of patients with acoustic neurinomas. In the early Karolinska Hospital experience,[16] patients were treated with doses as high as 125 Gy at the target center. It became evident that 90% of unilateral cases and 67% of bilateral cases could be controlled in terms of disease stabilization or regression by a dose of 20 Gy prescribed to the tumor surface; recent cases have been treated with 18 to 25 Gy. In Pittsburgh,[73] the incidence of trigeminal neuropathy consequent to radiosurgery was higher than expected, leading to a reduction in the dose prescribed to 16-18 Gy at the tumor margin. In both centers,[15,73] there was reduction in tumor volume in over 50% of lesions, with stable disease in 40 to 50%. Few patients have experienced an improvement in hearing following treatment. In the Pittsburgh series,[73] 62% of patients had some hearing in the treated ear, with 'useful' hearing in 48%, and complete deafness in 20% of patients. Other toxicity thus far has included mild trigeminal neuropathy in 15 to 20% of patients, and facial neuropathy which was often transient, and ultimately resolved completely, in 15 to 20%.[16,73] There was no relationship between the prescribed treatment dose or the minimum dose delivered to the tumor margin, and the risk of hearing loss and development of trigeminal or facial neuropathy. However, Flickinger et al.[73] found that there appeared to be a relationship between tumor size and complication rate; of 7 patients with tumors less than 10 mm in diameter, none developed complications. Noren et al.[15,16] no longer treat tumors greater than 30 mm in diameter. Radiosurgery appears to represent a valid treatment option for acoustic neurinomas, although the eventual clinical outcome in many of these patients remains to be seen.

Meningiomas

Conventional radiotherapy has been shown to improve local control in subtotally resected or recurrent meningiomas.[74] The results of conventional irradiation alone in gross unresectable disease have been poorer.[75] Several centers[30,53,68,76-78] have reported using radiosurgery to treat very small numbers of patients with small unresectable or recurrent lesions. In Heidelberg,[77] 17 patients were treated with doses ranging from 10 to 50 Gy prescribed to the 80% isodose surface; in all 13 patients in whom long term follow-up was available, disease remained stable. One patient with a relatively large meningioma was treated with a 73.6 cm^3 target volume, and died at 8 months post-treatment from herniation due to apparent necrosis within the meningioma. As a result, in Heidelberg, target volumes larger than 40 cm^3 are no longer treated. It was felt that a single fraction of 20 to 30 Gy prescribed at the tumor margin was sufficient to prevent further tumor growth. In Pittsburgh, 50 patients with meningiomas $\leqslant$ 35 mm, 34 of whom had had either a biopsy or subtotal resection and 16 of whom had meningioma diagnosed by neuroradiological criteria, were treated with the gamma unit.[78] A dose at the tumor margin of 10 to 25 Gy was delivered. The 2 year actuarial tumor control rate was 96%. Of 24 patients followed for 12 to 36 months, there was a reduction in tumor size in 13, and no change in tumor size in 9; there was growth of tumor outside the targeted volume in 2 patients. It was suggested that inability to include the entire tumor volume within the targeted volume may lead to treatment failure, and that 15 to 20 Gy delivered to the tumor margin may optimize control rates.

Although radiosurgery may represent a valid treatment option in selected patients with small, inoperable or recurrent lesions, optimal doses and target volumes, and ultimate control rates, have yet to be determined.

Craniopharyngiomas

Craniopharyngiomas may be cystic, solid, or both, and may cause hydrocephalus or symptoms or signs of compression of the pituitary, hypothalamus, or optic chiasm. Classical surgical management has included cyst drainage, and/or eventual complete microsurgical removal. Complete removal is associated with a significant risk of morbidity and mortality.[79] Conventional external beam irradiation may be administered after incomplete resection to reduce the risk of local recurrence.[79] Intracystic Yttrium-90 or Phosphorous-30 has been injected into cyst cavities to facilitate local control.[12]

Small numbers of patients with craniopharyngiomas have been treated with radiosurgery in a number of centers.[52,53,76] The largest series was at Stockholm,[19] where 36 patients have been treated with doses at the isocenter between 20 and 50 Gy, and dose at the periphery of solid tumor of no more than 10 Gy, and as low as 2 to 3 Gy; nevertheless, clinical results were described as 'excellent' and toxicity was minimal. Great caution, however, should be exercised in the treatment of tumors near the optic chiasm because of the potential concerns with injury of this structure with radiosurgery. Clinical data and further experience will determine the optimal dose and volume, and the ultimate role that radiosurgery will play in the management of craniopharyngioma.

Pituitary Adenomas

Since the early days of charged particle and proton radiosurgery, large numbers of patients with pituitary tumors have been treated at Berkeley,[68] the Soviet Union, and Boston.[80] Radiosurgery has been offered as primary non-invasive treatment, adjunctive radiotherapy for residual disease following surgical resection, and late recurrences following surgery. Excellent results of the use of protons in the treatment of acromegaly,[68,80] Cushing's disease,[50,68] and, in a smaller number of patients, Nelson's syndrome and prolactinomas[68] have been reported. A much smaller body of data has been published on photon-based radiosurgery.[19,30,32,52,76] At the Karolinska Hospital,[19] clinical remission was obtained in 76% of 90 patients with Cushing's syndrome treated with the gamma unit. Gamma unit or linac-based radiosurgery may indeed represent an alternative to charged particle techniques. In general, radiosurgery may be a useful adjunct in the treatment of selected patients with pituitary adenomas.

Malignant Tumors

The Heidelberg group[81,82] has reported the use of radiosurgery in 40 patients with solitary brain metastases, many from 'radioresistant' primary tumors, that had not previously been treated; the dose was 20 to 30 Gy prescribed at the 80% isodose surface. Of 26 patients with adequate follow-up, 11 had complete or partial reduction in the lesion and associated edema, with associated symptomatic improvement.[82] In their first 7 patients,[81] this response was very rapid, commencing within the first few days following treatment. Loeffler et al.[83] reported treating brain metastases recurrent following previous conventional external beam irradiation. In 21 lesions in 18 patients, 9 to 25 Gy was prescribed to the 70 to 90% isodose surface. The most rapid response was seen in metastatic adenocarcinomas, although reduction or stabilization of tumor volume and associated edema was seen in all 21 lesions. Motor deficits that were due to edema improved, whereas those due to lesions in the motor cortex did not. Of interest, most of their patients were left with a small enhancing ring with persistent edema at 1 year; biopsy in 1 patient revealed the presence only of tumor necrosis. At McGill University, 11 lesions in 9 previously irradiated patients were treated with radiosurgery. Partial or complete response was seen in all 11 lesions, with concomitant symptomatic improvement.[84] In general, treatment has been well tolerated.[81-84] Radiosurgery may be a valid palliative treatment option in the management of selected patients with brain metastases recurrent after conventional radiotherapy. The role that radiosurgery may play in the management of previously untreated brain metastases has not been established.

Several centers[30,32,51-53,76] have reported treating small numbers of patients with low and high grade astrocytomas, with stereotactic irradiation administered in one or multiple fractions. Patient numbers are very small, and followup short. In Vicenza,[51] 14 patients with low grade astrocytomas were treated in 1 to 2 fractions, using a stereotactic linac-based technique. Of these, 12 had a partial response on CT, and had clinical improvement. However, 8 patients had increasing edema at 2 to 12 months following treatment; a contrast enhancing ring appeared on CT in 5 patients. At McGill University,[53] 9 patients were treated with fractionated irradiation; 1 high grade and 7 low grade astrocytomas were treated primarily, and 1 high grade astrocytoma was treated for recurrence post-irradiation for palliation. Clinical improvement was seen in all patients with 3 being free of symptoms, beginning 2 to 3 months following irradiation. Radiological response has been much slower thus far, with tumor reduction in only 4 patients. Radiosurgical techniques may be helpful in the primary treatment of relatively localized, small low grade astrocytomas, and selected small recurrences of both low and high grade disease after conventional irradiation.

There may be a role for radiosurgery in the management of other, rarer neoplasms. There is a report of its successful use in the management of pineal tumors in a few patients.[13] Whilst proton beam techniques have treated many patients,[85] thus far it is only a proposal that the gamma unit be used to treat ocular melanoma.[86]

ACUTE AND LATE EFFECTS OF RADIOSURGERY

In conventional external beam radiotherapy, brain tolerance is related to the volume of tissue irradiated, the total dose administered, the size of dose fractions, and total time over which irradiation is delivered.[87] Despite the very small volumes that are treated, the single high dose fractions administered in radiosurgery have been of concern to some radiation oncologists. These volumes, and the total dose administered remain important parameters in determining the risk of significant adverse effects from radiosurgery.

Significant acute effects of therapy – i.e., those occurring within days to weeks of treatment – appear to be uncommon. Kjellberg et al.[88] reported that headache, elevated temperature (with treatment of diencephalic AVM's) and increased risk of seizures occurred in a few of their patients in the 24 hours following treatment. Loeffler et al.[89] reported transient aphasia beginning 12 hours post-treatment in one patient. Alexander et al.[90] correlated the incidence of acute nausea in radiosurgery patients with the dose that had been administered to the vomiting center, located in the floor of the fourth ventricle. Some centers admit patients for observation for 24 to 48 hours following the procedure. This is probably unnecessary in most cases, although it may be prudent to ask some patients to take nothing by mouth beginning the night before and to premedicate with anti-nauseants.

The early Stockholm experience[9] confirmed that radiosurgery in high doses produced small, well demarcated areas of brain necrosis – 'gamma lesions' – when it was administered to treat functional disorders. Wennerstrand and Ungerstedt[91] sectioned 9 brains of patients who had received 180 to 250 Gy for pain syndromes and found necrosis of brain tissue as early as 3 weeks following treatment. Leksell et al.[11] found that these lesions could be imaged as early as 24 hours post-treatment, in one patient. Arndt et al.[92] examined gamma lesions in animal brains, and divided pathological changes into: the necrotic stage, at 3 to 4 weeks after treatment; the stage of resorption, with chronic inflammatory cell infiltrate, up to 1 year following therapy; and the late stage, with prominent glial scar formation, at 1 year and beyond.

Marks et al.[63] reported the development of reversible white matter vasogenic edema in 5 patients 4 to 22 months after treatment with helium ions. Souhami et al.[60] reported similar changes in 2 patients treated with a linac-based radiosurgery technique. The group at Berkeley[63] also reported one case each of multifocal grey matter necrosis, and progressive large vessel vasculopathy as consequences of treatment. In Stockholm, Steiner et al.[18] reported an overall incidence of 7/300 (2.3%) of delayed brain necrosis 3 to 11 months following treatment of arteriovenous malformations. Kjellberg et al.[88] reported an incidence of complications of 10/709 (1.4%) in treated AVM patients. Coffey et al.[76] reported complications in 6/213 (2.8%) of their AVM patients. In the series of Loeffler et al.[89] 2/44 (4.5%) patients developed delayed radiation necrosis at 6 and 28 months following treatment. Steiner et al.[17] reviewed their data and found more frequent complications with increases in dose, suggesting a possible threshold prescribed dose of 20 Gy with an 8 to 14 mm collimator, with their gamma unit. Kjellberg[93] established proton isoeffect curves, plotting 1% and 99% brain necrosis incidence lines with respect to dose and beam diameter. Flickinger[94] identified the difficulties in applying these curves to photon radiosurgery, and introduced the integrated logistic model for the prediction of complication rates with respect to dose and treatment volume. Flickinger et al.[95] later generated dose-volume isoeffect curves using this formula for linac and gamma unit radiosurgery, and found them to be similar. The linac curve for the 3% risk of necrosis was also found to be similar to Kjellberg's proton 1% necrosis curve.[95] Flickinger and Steiner[96] modified the formula for response to doses higher than 130 Gy, using data from Stockholm. Only extensive clinical experience will indicate whether these dose-volume curves actually predict for late complications.

Other factors may influence the risk of significant late effects. Kjellberg et al.[88] found that they were able to reduce the incidence of complications over time by reducing the dose in patients with prior neurologic deficits, in whom injured brain may have a lower threshold for damage, and in those AVM's that were large or adjacent to neurologically active areas. Backlund et al.[14] considered the tolerance of any portion of the optic tracts to radiosurgery to be 10 Gy, and planned treatment to pituitary lesions accordingly. Kondziolka et al.[78] suggested that the tolerance of some cranial nerves to radiosurgery may differ from that of others, as the incidence of new neuropathies in treated meningiomas was 4%, in contrast to the much higher incidence of trigeminal and facial neuropathy in treated acoustic neurinomas.

Loeffler et al.[89] certainly were not prepared to use radiosurgery to treat lesions in previously irradiated critical regions of the brain. Nevertheless, there are no data on the tolerance of such structures as brain stem and optic nerve to the very small volumes treated in radiosurgery. Currently, the treatment volume, its location relative to critical structures, the lesion to be treated, and any previous irradiation to the brain all must be considered in determining the dose and target volume with which to treat. It appears, however, that radiosurgery is relatively safe, with infrequent significant treatment related morbidity relative to the potential morbidity of such lesions as untreated AVM's.

CONCLUSIONS

Charged particle radiosurgical techniques are preferable in the treatment of larger intracranial lesions, but will never be widely available because of high cost. Gamma unit and linac radiosurgery are comparable to each other in terms of accuracy and dose distribution. Advantages to radiosurgery with a modified linear accelerator include much lower capital and maintenance costs.

The results of treatment with all of these techniques appear to be very similar. Radiosurgery is now a major treatment modality for arteriovenous malformations that are inoperable, acoustic neurinomas, craniopharyngiomas, and small, inoperable or recurrent meningiomas. Its role in the management of selected, small malignant primary or metastatic tumors in the brain, either primarily or after they recur following previous cranial irradiation, has yet to be fully defined.

These techniques appear to be associated with infrequent significant early or late morbidity; the relationship between the incidence of these complications, and dose, target volume, and proximity to adjacent critical structures will only be elucidated by further clinical experience and detailed reporting of complications. Similarly, interpretation of these and other results of treatment can only be made with reports of the location and size of treated lesions and complete descriptions of dosimetry, including minimum and maximum dose to the target volume. Efforts to improve the therapeutic ratio may include isodose volume shaping techniques and fractionated treatment using stereotactic techniques.

Concerns have been expressed regarding the proliferation of radiosurgery facilities, because of the fact that many centers in which neuropathology is not an area of particular expertise may treat patients with radiosurgery and obtain poor treatment results.[20,54] Certainly, the cooperative efforts of a skilled and experienced interdisciplinary team, including neurosurgeons, radiation oncologists, neuroradiologists, and medical physicists, and diligent quality assurance at all times, are necessary to optimize these results. If such efforts are made, radiosurgery will continue to be an important tool in the management of several intracranial lesions.

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