**Current Status and Optimal Use of Radiosurgery**

*Review Article* [1] | February 01, 2001
By Steven D. Chang, MD [2] and John R. Adler, Jr, MD [3]

The field of stereotactic radiosurgery is rapidly advancing as a result of both improvements in radiosurgical equipment and better physician understanding of the clinical applications of stereotactic radiosurgery. This

**Introduction**

Radiosurgery combines stereotactic techniques (to achieve precise three-dimensional localization) with highly focused high-energy radiation treatments. This procedure makes it possible to deliver a very large dose of radiation to a small target while minimizing the dose outside the target volume. A previous report surveyed the clinical results and complications associated with radiosurgery for the treatment of metastatic tumor, primary glioma, arteriovenous malformation (AVM), and benign conditions including pituitary tumor, acoustic neuroma, and meningioma.[1]

Over the past several years, however, radiosurgery has advanced rapidly. Physicians now have a better understanding of the use of radiosurgery in the treatment of brain metastases, including whether or not the addition of whole-brain irradiation provides any advantage over stereotactic radiosurgery alone. Large AVMs, previously considered difficult to treat, are now routinely treated with radiosurgery either through staged treatments or as part of a multimodality regimen. Radiosurgery has also evolved as a potential therapy following standard radiation for nasopharyngeal carcinoma. Improved local control and survival rates have been reported for this common cancer.

Advances in both technique and radiosurgery equipment have led to the use of hypofractionated radiosurgery in selected cases (which is believed to reduce patient morbidity) and frameless image-guided radiosurgery (which has resulted in both increased flexibility of treatment, as well as treatment of lesions outside the head). The following discussion focuses on our experience with these radiosurgical advances at Stanford University.

**Advances in the Treatment of Brain Metastasis**

**Stereotactic Radiosurgery**

Stereotactic radiosurgery has emerged as a treatment for patients with brain metastasis, either with or without whole-brain radiation therapy (WBRT), with an 85% to 95% control rate.[2-7] Median survival after radiosurgery (6.4 to 10 months)[3,4,6-12] is comparable to survival rates that have been reported with surgical resection followed by conventional fractionated radiotherapy (4 to 13 months),[13,14] with good local control.[3,4,6-8,10-12,15,16] Recent studies have shown that patients treated with radiosurgery for either one or two brain metastases have a prolonged survival similar to that achieved with surgical resection.[2,5,9]

The success of stereotactic radiosurgical treatment of brain metastases has raised the issue of whether WBRT in conjunction with radiosurgery represents a treatment advantage over radiosurgery or WBRT alone. Reporting a series of 105 patients treated from 1991 to 1997, Sneed et al observed that response rates with radiosurgery alone were not statistically different from those achieved with radiosurgery plus WBRT, with respect to freedom from progression (71% vs 79%) and median survival (11.3 vs 11.1 months).[17] In contrast, Fuller et al reported a series of 27 patients with 41 metastatic tumors and noted that radiosurgery plus WBRT achieved statistically superior disease control ($P = .0007$), compared with radiosurgery alone.[18]

In a review of 97 patients who had been treated for two to four brain metastases, Schoeggl et al
concluded that stereotactic radiosurgery provided an equivalent rate of survival, compared to the historic experience of patients treated with WBRT.[19] However, their review did not compare a subset of patients treated with radiosurgery alone to those treated with radiosurgery plus WBRT.

Kondziolka et al reported a randomized trial of WBRT vs radiosurgery plus WBRT, which showed that WBRT combined with radiosurgery in patients with two to four brain metastases significantly improved the control of brain disease.[20] The 1-year rate of local failure was 8% for radiosurgery and WBRT combined, compared to 100% for WBRT alone. The median survival with WBRT alone was 7.5 months, compared to 11 months for WBRT plus radiosurgery. While the median time to local failure and time to any brain failure were statistically significant ($P = .0005$ and $.002$, respectively), median survival was not statistically different, perhaps because of the relatively small number of patients ($N = 27$) in the study.

**Stanford Treatment Algorithm**

Based on our own experience and that of other institutions, a fairly well-established algorithm for treating patients with multiple brain metastases is followed at Stanford.[21] Whole-brain irradiation is the preferred treatment for patients with progressive systemic disease, poor performance status, or more than four lesions. Patients with multiple lesions who undergo WBRT and have a subsequent reduction in the radiographic number of metastases may be candidates for a stereotactic radiosurgical boost to the residual tumors if there are four or fewer lesions.[3,22] Patients with stable systemic disease and a good performance status but who have mass effect from one or more tumors are candidates for surgical resection of their symptomatic lesions, with radiosurgery or radiation therapy used for the remaining smaller tumors. Patients with stable systemic disease, a good performance status, and no mass effect from their brain metastases (four or fewer tumors) are optimal candidates for stereotactic radiosurgery.[22] A 91% tumor control rate has been observed in this population.[3]

At our institution, most patients undergoing radiosurgery for multiple brain metastases are treated with WBRT and radiosurgery, whereas patients with a single brain metastasis are often treated with radiosurgery alone. Whole-brain irradiation is reserved for tumor recurrence/progression and new brain tumors associated with a poor performance status or progressive systemic disease. Unlike conventional brain irradiation, radiosurgery can be repeated for metachronous lesions months to years after initial treatment.

**Multimodality Treatment of AVMs**

Stereotactic radiosurgery is an excellent treatment for small to moderately sized AVMs, particularly those located in surgically inaccessible regions or in patients who are poor candidates for surgery.[23-26] Such obliteration typically takes place over 2 to 3 years. Arteriovenous malformations less than 4 cm in diameter treated with 20 to 25 Gy have a 3-year obliteration rate of 76% to 95%, with low morbidity (2.5% to 4.5% of patients develop permanent neurologic deficits; 2.5% to 4.5%, transient deficits).[23-30]

Although radiosurgical treatment of smaller AVMs is routine, larger AVMs often present a greater challenge. Arteriovenous malformations greater than 4 cm in diameter have only a 33% to 50% rate of obliteration at 3 years after radiosurgery but a 20% to 30% complication rate following treatment at doses of 15 to 20 Gy.[23,25,26] The rate of obliteration increases for larger AVMs with the use of higher doses (25 to 45 Gy), but the risk of radiation-induced complications also increases.

Overall treatment morbidity for large to giant AVMs can be reduced with multimodality therapy—ie, combinations of embolization, stereotactic radiosurgery, and microsurgery.[31,32] Our previous experience with large and complex AVMs has shown that such multimodality therapy can reduce patient morbidity and mortality.[31]

Embolization obviously reduces the nidus volume requiring resection, but having had stereotactic radiosurgery several years prior to surgical resection also produces a benefit. In some patients,
Some authors have recommended staged stereotactic radiosurgery when treating large AVMs.[33] In these cases, multiple radiosurgery treatments are delivered to different portions of the AVM at various time intervals to avoid delivering treatment to a single large target, thereby theoretically reducing the risk of radiation necrosis. This option has been applied in selected patients.[31,34] The disadvantages of such an approach are the second latency period of 1 to 3 years before obliteration occurs, the possibility that a second radiosurgery treatment may still not obliterate the AVM, and the risk of radiation-induced injury, which may be higher with a second radiosurgery treatment.

**Stereotactic Radiosurgery Boost for Nasopharyngeal Carcinoma**

Nasopharyngeal carcinoma arises in the mucosa or submucosa of the nasopharynx, and frequently spreads to the skull base. Given the radiosensitivity of the tumor, radiotherapy is the primary treatment. However, there is a significant incidence of local failure (26% to 100%) in more advanced cases after treatment with conventional radiotherapy.[35-37] Although higher radiation doses or brachytherapy boosts increase local control,[35,37-40] the possibility of normal tissue injury and/or the inability to effectively treat tumor extension to the skull base limit the usefulness of these techniques. Because of the historically high local failure rate, we developed a protocol to deliver a planned stereotactic radiosurgical boost following conventional radiotherapy in patients with nasopharyngeal carcinoma.

From October 1992 to December 1998, 23 patients at Stanford University Medical Center underwent radiotherapy followed by planned radiosurgery as initial management of a newly diagnosed, biopsy-proven nasopharyngeal carcinoma. The total dose of radiotherapy to the nasopharynx was 66 Gy, divided into daily treatments of 200 cGy. Elective neck irradiation to a dose of 50 Gy was also used; involved lymph nodes received radiation boosts to a total dose of 66 Gy. In addition to the radiotherapy, 15 patients received cisplatinum-based chemotherapy.

Within 4 weeks of completing radiotherapy, patients were treated with radiosurgery. Treatment was administered with one to four isocenters, depending on tumor volume and shape. The prescribed dose of radiation was delivered to the periphery of the original lesion, corresponding to the 80% to 85% isodose contour. The median dose was 12 Gy (range: 7 to 15 Gy). Mean follow-up was 27 months (range: 8 to 72 months), with 12 patients followed for more than 2 years, and 7 patients followed for more than 3 years.

**Stanford Study Results**

Throughout the course of follow-up, there were no local recurrences among the 23 patients treated with radiosurgery (Figure 1). Cervical lymph node recurrences developed in two patients, and seven patients developed distant metastases including liver (1), lung (2), and bone (4). Of these seven patients, four expired as a result of their metastases.

Simultaneous cisplatin (Platinol)-based chemotherapy and radiotherapy followed by radiosurgery was administered to 15 patients. No significant difference in relapse-free survival was observed, but a trend favored the chemotherapy group: Actuarial relapse-free survival at 3 years was 59% among patients receiving chemotherapy and radiotherapy followed by radiosurgery, compared to 37.5% in the patients who were treated with radiotherapy or radiosurgery alone. No patient developed either acute or late complications following radiosurgery.

**Study Conclusions**

Our preliminary experience showed that a high rate of local control can be achieved with stereotactic radiosurgery even in patients with advanced-staged nasopharyngeal carcinoma. We believe that radiosurgery is more effective than brachytherapy in such cases because of the ability of radiosurgery to effectively treat the base of skull. Although intracavitary brachytherapy in the nasopharynx is likely to be effective in treating tumors confined to the mucosa or submucosa, it is unlikely to eradicate a larger mass that extends several centimeters beneath the mucosal surface.
Radiosurgery not only provides the same benefits as brachytherapy (i.e., relative sparing of normal tissues and the ability to safely boost regions of involvement to high doses), but it can also deliver a high radiation dose to sites that are remote from the nasopharynx.

Although longer follow-up is needed, radiosurgery following radiation has resulted in 100% local control of nasopharyngeal carcinoma in a small group of patients. Based on this experience, patients with advanced nasopharyngeal carcinoma treated at Stanford receive a 66-Gy dose of radiation with concurrent cisplatin chemotherapy, followed by 12-Gy radiosurgery to the primary site, after which three more cycles of cisplatin/fluorouracil chemotherapy are administered. Despite the benefits of this approach, it is obvious that more effective chemotherapy is needed to decrease the incidence of late systemic recurrence in this patient population.

**Fractionated Stereotactic Radiosurgery**

The majority of tumors within the central nervous system can be treated with stereotactic radiosurgery in a single fraction. However, some targets, including acoustic neuromas and tumors adjacent to or surrounding the optic apparatus abut critical cranial nerves, which places these neurologic structures at risk of irradiation despite a rapid falloff of dose outside the tumor.

Fractionated radiosurgery evolved from a belief that fractionated therapeutic radiation (delivery of the total therapeutic dose in several smaller fractions) enhances tumor susceptibility and allows for the recovery of normal tissues, thereby increasing tumor control while minimizing the effect on normal tissues. Our experience with fractionated radiosurgery has focused on the treatment of acoustic neuromas and tumors adjacent to the anterior visual pathways.

Fractionated radiosurgery is effective for small- and moderate-sized acoustic neuromas, with tumor control rates of 90% to 95% at 5- to 10-year follow-up.[41] However, most radiosurgery studies report preservation of useful hearing in less than 60% of patients.[41-44] Our recent experience at Stanford in treating 33 patients with acoustic neuromas using fractionated frame-based linear accelerator (LINAC) radiosurgery (three 7-Gy fractions spaced 24 hours apart) has produced 97% tumor control, with 77% of patients maintaining useful hearing at 2-year follow-up.[45] While these findings are preliminary, they suggest that fractionated radiosurgery may increase the probability of maintaining useful hearing without any decrease in tumor response to radiosurgery.

Since this published experience, we have noted similar responses with respect to tumor control and hearing preservation associated with use of the CyberKnife, a frameless image-guided system for delivering radiosurgery (see below). We have also utilized hypofractionated, image-guided stereotactic radiosurgery for the treatment of lesions in proximity to the anterior visual pathways (optic nerves and chiasm). Although the incidence of optic neuropathy after radiosurgery is thought to be related to many factors, including total dose, fraction size, and volume treated, we believe that fractionated radiosurgery decreases the overall incidence of optic neuropathy.

Since 1997, we have treated 16 patients with lesions (including meningioma, optic glioma, and optic metastases) in close proximity (< 1 mm) to the anterior visual pathways. Two to five fractions were prescribed with a minimum interfraction interval of 24 hours. No disease progression or visual deterioration has been observed within the treatment field at a mean follow-up of 14 months. Although a longer follow-up will be necessary to determine the clinical benefit of fractionated radiosurgery for anterior visual pathway lesions, our preliminary experience has shown that there may be a decreased risk of optic neuropathy with this method.

**Image-Guided Stereotactic Radiosurgery**

A rigid external frame attached to the skull has conventionally been used to establish precision guidance for stereotaxis when determining the spatial coordinates of an intracranial target. The immobilization required for stereotactic localization is typically provided by skeletal fixation. The primary drawback in the radiosurgical patient who is awake is that such devices are necessarily associated with some degree of pain. Thus, even though fractionated radiosurgery is theoretically attractive in many clinical situations, the associated pain may make it cumbersome. In particular,
because of the discomfort caused by frames, children must be treated under general anesthesia.

Several "noninvasive" frames have been developed that rely on dental molds and/or bony prominences to anchor an external frame of reference to the head that can be reattached without much difficulty.[46-48] However, the use of these less-invasive devices entails some compromise in accuracy. Also, such instruments are poorly adaptable to edentulous adults or children who cannot reliably cooperate. Finally, and perhaps most importantly, all radiosurgical frames are designed to work only in and around the head, and the principles they incorporate are difficult to apply to extracranial locations.

The CyberKnife

An alternative to strict immobilization is to track the target in real time, a solution that calls for more complex technology. Such a method for performing precision irradiation, called image-guided radiosurgery, does not require an external frame and is sufficiently generic to be modified for application throughout the body.[49-56] This concept is incorporated in the CyberKnife (Accuray, Inc; Sunnyvale, Calif), a frameless, image-guided radiosurgical device that is currently available at nine medical centers worldwide (Figure 2).

Editor's Note: Drs. Chang and Adler are shareholders in Accuray.

Basic Components of the Device: The CyberKnife combines two advanced technologies to deliver frameless conformal radiosurgery. The first is a lightweight (285 lb) 6-MV linear accelerator designed for radiosurgery and mounted to a highly maneuverable robotic system, which can position and point the LINAC with a mean total radial error of 1.6 mm, and a mean positioning error along each coordinate axis of ±0.9 mm.[57]

The second innovation is near real-time image guidance, which eliminates the need for skeletal fixation to either position or rigidly immobilize the target. This system acquires radiographs of the treatment site’s skeletal features, uses image registration techniques to determine the treatment site’s coordinates with respect to the LINAC, and transmits the target coordinates to the robot, which then directs the beam to the treatment site. When the target moves, the process detects the change and corrects beam pointing in near real time.

Two fixed diagnostic fluoroscopes, illuminated by x-ray sources 365 cm away and arranged orthogonally with respect to the patient, comprise the imaging hardware. They provide a stationary frame of reference for locating the patient’s anatomy, which, in turn, has a known relationship to the reference frame of the robot and LINAC.

The CyberKnife determines the location of the skull or spine in the coordinate frame of the radiation delivery system by comparing digitally reconstructed radiographs derived from the treatment planning images with radiographs acquired by the real-time imaging system. Once skeletal position is determined, the coordinates are relayed to the robot, which adjusts the pointing of the LINAC, and radiation is delivered. The speed of the imaging process allows the system to detect and adjust to changes in target position in less than a second. The LINAC is then moved to a new position, and the process is repeated.

Homogeneous Dose Delivery: Conventional radiosurgical systems only allow for isocentrically based treatments. Because the resulting region of high-dose delivery is spherical,[58-60] treatment of nonspherical lesions is problematic. "Sphere packing," as typically done with standard radiosurgical devices, results in some measure of both overtreatment in normal tissue and undertreatment within the target.

The CyberKnife, however, enables the delivery of a more homogeneous treatment dose. First, regions of interest are delineated on computed tomography or magnetic resonance images, and the amount of radiation that each can tolerate is specified. Next, the system uses the contour data to create a three-dimensional representation of the tumor geometry, and based on this, the system defines an initial set of beam configurations.
Finally, optimization techniques are used to determine dose weighting of the beams to satisfy the specified dose constraints. If the constraints cannot be satisfied in the context of initial beam selection, information gained during optimization is used to select a new set of beam configurations more likely to satisfy the constraints. This iterative process of beam selection and optimization continues until the system finds a feasible solution. The CyberKnife then calculates the dose distribution and presents the plan for review.

During the actual treatment, the LINAC stops at each of approximately 250 to 300 equally spaced nodes. The treatment beam is not constrained to point at the center of the sphere, but can be aimed anywhere within a volume around the center. This allows delivery of nonisocentric beams aimed at points within the target that are not at the center of the sphere, thus resulting in markedly improved target conformality and dose homogeneity. Total treatment time depends on the complexity of the plan and delivery paths, but is comparable to standard LINAC treatments. Because skeletal fixation is not required, fractionation is possible with minimal patient discomfort.

**Experience With the Device:** As of November 2000, more than 1,000 patients with benign and malignant intracranial tumors have been treated with the CyberKnife at Stanford Medical Center and eight other sites worldwide. In addition to the intracranial treatments, 11 cervical lesions, including seven intramedullary spinal cord tumors or vascular malformations, received treatment at Stanford. Radiosurgery of the cervical region has been performed by using the vertebral bodies as points of radiographic reference and spatial location. To date, the outcome for all lesions (as defined both clinically and radiographically) equals that achieved with standard radiosurgery.

**Extracranial Lesions:** A primary objective of the development of image-guided radiosurgery was the ability to treat extracranial lesions. With the implementation of a new camera system (amorphous silicon detectors), achieving this goal became feasible. Since most extracranial lesions within the thorax and abdomen move with respiration—ie, are not fixed with respect to bony structures—a system for target localization was developed that relies on implanted fiducials, respiratory gating, and target tracing using infrared, transduced chest and abdominal wall respiratory movement.

Several metal implantable fiducials with the requisite characteristics to be readily imaged by the CyberKnife have been identified. For example, gold spheres 2 to 3 mm in diameter can be successfully sutured to soft tissue within the abdomen, allowing the targeting of abdominal cancers. Alternatively, smaller gold balls can be implanted with a 14-gauge needle,[61] or gold wires (1-mm diameter) can also been used.[62]

For spine fiducials, small bone screws anchored to the spine through stab incisions can provide an acceptable level of contrast relative to bone. While fiducials fixed to bone can be assumed to maintain their relative position, it is unclear whether markers attached to soft tissue can migrate. Studies are underway to investigate the issue of fiducial migration within soft tissue.

Thus far, five patients with thoracolumbar lesions (bone metastases or schwannomas) have been treated with the CyberKnife (Figure 3). All of these patients had 4-mm screw fiducials implanted into the spine through stab incisions. Four pancreatic tumor patients underwent implantation of gold fiducial balls during a laparotomy for pancreatic carcinoma. These patients were treated with a highly conformal single fraction of 15 Gy using breath-holding throughout the procedure (Figure 4). Administered as part of a dose-escalation protocol, the treatment provided significant palliation from pretreatment symptoms. A similar protocol was used to treat three patients with primary pulmonary carcinoma following percutaneous implantation of fiducials adjacent to the lesion.

**Conclusions**

Radiosurgery has been established as a safe and effective method for treating selected small tumors and AVMs of the brain. For such lesions, the modest risk of complication from radiosurgery compares favorably with open surgery. Refinements in technique have resulted in improved patient outcomes and reduced morbidity for intracranial targets. The development of frameless image-guided radiosurgery will further increase the application of stereotactic radiosurgery through increased
flexibility of use for both intracranial targets and lesions outside the head.

References:


Source URL: http://www.psychiatrictimes.com/current-status-and-optimal-use-radiosurgery

Links: