CyberKnife Radiosurgery in Neurosurgical Practice

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Abstract: Gamma Knife radiosurgery revolutionized neurosurgical care for intracranial tumors, arteriovenous malformations, and functional disorders. A new generation of radiosurgical devices exemplified by the frameless, image-guided, robotic CyberKnife (Accuray, Inc, Sunnyvale, CA) extends the benefits of precise, stereotactic delivery of ablative doses of radiation to the spine and other extracranial targets not easily treated by the Gamma Knife. In this review, CyberKnife technology and applications in neurosurgery are described. Eliminating the stereotactic frame allows the CyberKnife to provide a far more comfortable treatment experience for patients and makes it easier to treat lesions in multiple sessions, thereby extending to radiosurgery the potential radiobiologic benefits of dose hypofractionation. Robotic radiation delivery allows treatment plans to be nonisocentric, conforming more readily to complex, nonspherical lesion volumes. The ability to treat extracranial sites may be a significant benefit to neurosurgeons because institutions may be more likely to adopt radiosurgical technology that has applications beyond neurosurgical practice.

Key Words: stereotactic radiosurgery, robotic radiosurgery, metastases, benign tumors, trigeminal neuralgia, arteriovenous malformation

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It is not an overstatement to assert that stereotactic radiosurgery revolutionized the practice of neurosurgery. The concept of radiosurgery was introduced by Leksell[1] in 1951. The device responsible for the rapid adoption of radiosurgery across the world was the Gamma Knife. The Gamma Knife was the first device to deliver highly focused beams of radiation to precisely targeted intracranial lesions without damaging the surrounding brain tissue. This ability is predicated on the fact that intracranial lesions do not move within the skull. The lesions can, therefore, be precisely localized with reference to a stereotactic frame that is rigidly affixed to the skull with metal screws. For the first time in surgical history, the Gamma Knife provided an alternative to surgical resection of lesions that were difficult to reach if not inoperable. Even for lesions that were operable with reasonable safety margin, the Gamma Knife provided a noninvasive and effective treatment. It is not surprising that such a remarkable technological advance won wide adoption across the world soon after its introduction. Since then, the Gamma Knife has established a long record of successful treatment of intracranial lesions to include brain tumors, vascular malformations, and trigeminal neuralgia.[2]

Despite its highly successful history, the Gamma Knife has 2 major limitations. First, to precisely reference an intracranial lesion for targeting, a stereotactic frame must be attached to the patient's head and that frame is then fixed within the Gamma Knife helmet. This feature of the Gamma Knife is responsible for its most significant limitation, which is its inability to treat lesions outside the cranium.

Eliminating the skull frame *alone* would significantly reduce the pain and discomfort associated with radiosurgery. However, a radiosurgical system that could escape the constraints of the skull frame *and* deliver the proven efficacy of radiosurgical treatment to lesions outside of the cranium would greatly expand radiosurgical indications, and could potentially revolutionize the surgical management of tumors throughout the body. The CyberKnife overcomes these limitations of the Gamma Knife. Just as the Gamma Knife revolutionized the practice of intracranial neurosurgery, the CyberKnife is poised to revolutionize the practice of general surgical oncology, urology, thoracic oncology, and gynecologic oncology. Within the field of neurosurgery, the CyberKnife will build upon the established familiarity of neurosurgeons with intracranial radiosurgery to rapidly apply the promising technology to spinal tumors. Because the CyberKnife provides a more comfortable treatment experience for patients undergoing intracranial radiosurgery and because it extends the proven benefits of radiosurgery to spinal pathology, it will be important for all neurosurgeons to understand the technological underpinnings of CyberKnife radiosurgery and the indications for its use in neurosurgery.

CYBERKNIFE TECHNOLOGY

Radiation Delivery

In simplest terms, the CyberKnife consists of a linear accelerator (LINAC) attached to an industrial robot (Fig. 1). The robot moves the linear accelerator to multiple predetermined points in space around the patient. At each point in space, or *node*, the CyberKnife may deliver a burst of radiation through a 6MV LINAC.

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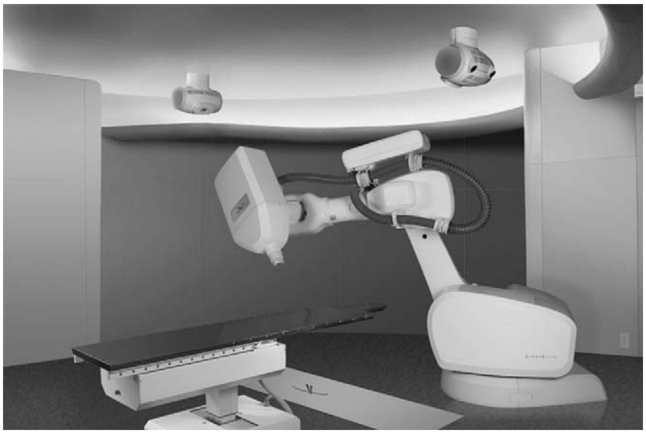

FIGURE 1. CyberKnife G4 model.

The technique is similar to the Gamma Knife in that multiple beams of radiation are targeted at a lesion from different trajectories so that the radiation dose is concentrated on the lesion and falls off abruptly outside the lesion, thereby sparing the surrounding tissue from a concentrated dose of radiation. The Gamma Knife accomplishes this by using a selection of 201 apertures, which are opened simultaneously. The CyberKnife delivers individual beams sequentially over time. A significant advantage of the CyberKnife delivery system is that it is not limited to 201 treatment beams. In fact, the CyberKnife can deliver radiation beams from an infinite number of nodes in space around a lesion (Fig. 2). For planning purposes and for computational simplicity, the CyberKnife is limited to 1200 different beam directions, 6 times as many as the Gamma Knife. A different treatment plan will generate different beam directions as necessary to produce the desired dose distribution, and small patient movements lead to adjustments in beam directions as needed to track the tumor. Thus, an infinite number of beam directions is possible with the CyberKnife, a feature that leads to flexibility in dose delivery that is unequaled by other radiosurgery systems.

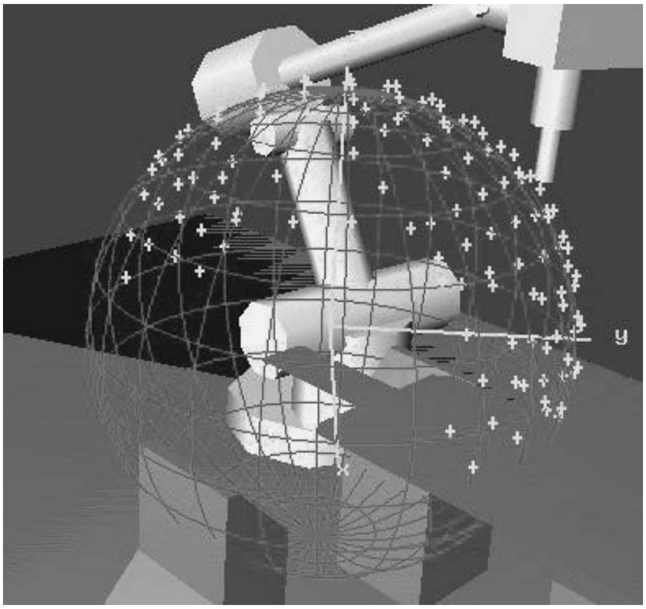

FIGURE 2. Node geometry. The CyberKnife treatment planning system directs beams at the target from multiple directions originating at nodes arranged in a sphere around the patient.

Another important distinction between the CyberKnife and the Gamma Knife concerns the shape of the treatment volume. The design of the Gamma Knife requires all beams to be focused on a single point called the *isocenter*. The individual CyberKnife treatment beams are not constrained in this fashion, but rather can deliver treatment beams nonisocentrically. This is a significant advantage when treating nonspherical lesions; to treat such lesions with the Gamma Knife, multiple isocenters are used in a process sometimes referred to as sphere packing. Each individual isocenter requires a repositioning of the patient in the treatment helmet. To visualize this concept, consider the farcical treatment of a 6-cm hotdog (Fig. 3). Using the Gamma Knife, one may treat the hotdog using 3 overlapping isocenters the size (about 2 cm) and shape of ping-pong balls aligned along the hotdog. A CyberKnife treatment would not use any isocenters, but instead would use a selection of the 1200 available beams to cover the entirety of the hotdog. One beam may be directed at the north pole of the hotdog, another beam directed at the south pole, and many other beams (perhaps a hundred or more) would be directed along the length of the hotdog.

Both the Gamma Knife and the CyberKnife use collimators to regulate the width of each individual radiation beam. Because the beams of the Gamma Knife all converge on an isocenter, Gamma Knife collimators ultimately only regulate the size of the ping-pong ball. That ping-pong ball (or isocenter) is the ultimate unit of radiation delivered. The CyberKnife's nonisocentric

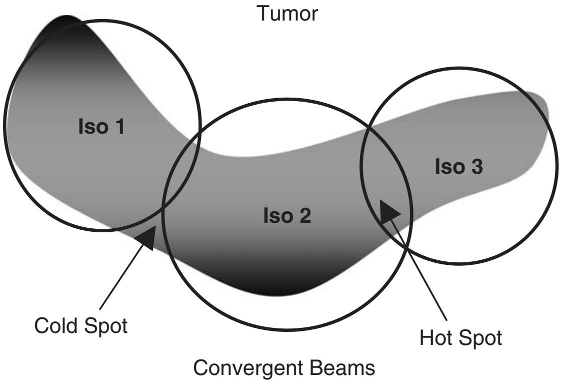

FIGURE 3. Isocentric treatment planning. The use of multiple, spherical isocenters can result in dose inhomogeneity characterized by hot and cold spots within the treatment volume. Nonisocentric treatment planning can produce more homogeneous dose distributions.

dosing capacity makes the individual beam the smallest unit of dose delivery. Although the Gamma Knife would treat our 6-cm hotdog with three 2-cm isocenters the CyberKnife could treat the hotdog with 200, 5-mm beams of radiation.

The ping-pong ball/hotdog analogy raises another important point. In an ideal dose distribution, the volume of the prescription dose would match the volume of the lesion. The Gamma Knife's ping-pong ball doses would result in areas of overlap of the ping-pong balls, that is, regions of the hotdog would receive much higher, even excessive doses of radiation. Inevitably, there would also be areas within the volume of the hotdog that would not be covered even with the densest packing of ping-pong balls. Those areas may receive a less-than-adequate dose of radiation. The technical term for hot spots and cold spots within the treated volume is dose inhomogeneity. The 1200-plus beams of nonisocentrically targeted radiation of the CyberKnife versus the 201 isocentrically targeted beams of the Gamma Knife offer the potential for much greater dose homogeneity with the CyberKnife than with the Gamma Knife. Figure 4 shows from a 3-dimensional treatment-planning image (1) that hundreds of beams directed at the lesion (represented by each color) are selected by the treatment planning software, (2) that the portion of them (depicted in light blue) that best covers the lesion while avoiding critical structures is actually delivered by the system, and (3) that the beams that course through the eye and optic tract are excluded (red lines).

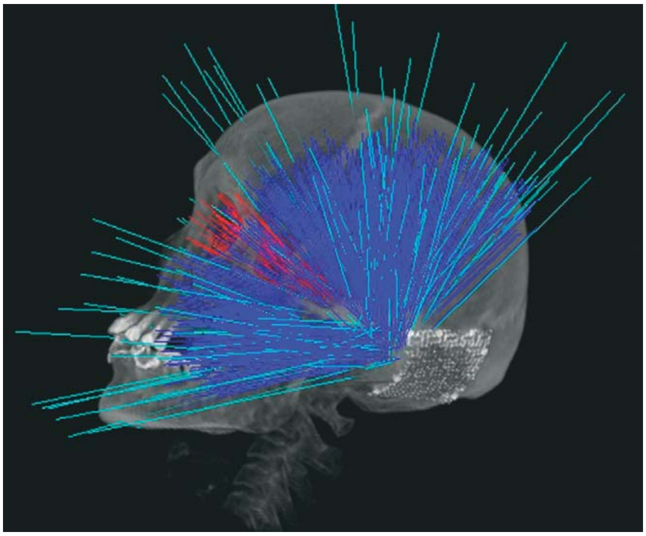

FIGURE 4. Three-dimensional depiction of treatment planning solution. All treatment beams are indicated by lines moving through the treatment volume. The light blue lines represent beam directions actually delivered by the system, the darker blue lines show directions not delivered, and the red lines show beam directions explicitly prohibited by the user because they pass through a critical structure (eye and optic tract).

A final advantage of the CyberKnife that follows from the elimination of the stereotactic frame is the ability to conveniently treat patients in multiple sessions, or fractions. The Gamma Knife frame made treatment over successive days very difficult, but because the CyberKnife targets lesions using bony or other fixed frames of reference, accurate repositioning of the patient in the treatment field is quickly accomplished and lesion targeting and tracking proceed as planned on each successive treatment day. The potential benefits of dose hypofractionation have only begun to be investigated, but the motivation to treat in fractions is the desire to treat lesions near or adjacent to sensitive critical structures such as cranial nerves or the spinal cord (or radiosensitive organs in the case of non-neurosurgical applications). Consider radiosurgical treatment of acoustic neuromas.[3] It is reasonable to hypothesize that fractionating radiosurgery could increase rates of hearing preservation by spreading the radiation dose to the cochlear nerve over several days, thus allowing for reparative processes between treatment sessions. Staging radiation delivery may also enhance tumor susceptibility to radiation by allowing for the oxygenation of tissues between sessions. The radiobiology of these claims has yet to be proven, but recent reports of successful treatment of intracranial and spine lesions supports a role for hypofractionation in stereotactic radiosurgery.

Targeting Mechanism

The CyberKnife employs a powerful localization and targeting system. Extensive technical reviews of the subject are available.[4,5] The reference coordinates for intracranial lesions are provided by the contour of the skull on the planning computed tomography (CT) images. For spinal lesions, the targeting is provided by implanted radiopaque markers (fiducials) or by the contours of the vertebral column in the spine. There is a real-time control loop between imaging and beam delivery, which allows the aiming of the beams to adjust to a moving target. The position of the skull, fiducials, or spinal bony landmarks is determined repetitively throughout treatment by orthogonal x-ray cameras and detectors positioned on either side of the patient. The images are registered by a computer to digitally reconstructed radiographs (DRRs) derived from the treatment planning CT. This allows the position of the treatment site to be translated to the coordinate frame of the LINAC. If the patient moves between one beam delivery and the next, adjustments are made to assure that targeting remains accurate. This linkage of real-time imaging of the bony landmarks or fiducials that register the lesion in space to the robotic treatment arm that delivers the individual beams of radiation to the targeted lesion is the critical technological advance that allowed radiosurgery to escape the confines of a rigid skull frame. The overall accuracy of dose delivery using this technique has been reported to approximate the accuracy of frame-based radiosurgical dose delivery.[6,7]

Treatment Process

Like the Gamma Knife, decisions regarding CyberKnife radiosurgical treatment should be made by the patient in consultation with both a radiation oncologist and a surgeon. Initially patients may consult with either medical provider; if the initial provider determines that radiosurgery is appropriate, the patient should then be referred to the other provider in this 2-member team for further consideration. In these paired encounters, the surgeon should be responsible for discussing surgical alternatives to radiosurgery and the potential risks of damage to structures surrounding the lesion. The surgeon should also determine whether a diagnostic biopsy is necessary before radiosurgical intervention. The radiation oncologist should be responsible for discussing alternative therapies of standard radiation therapy. The radiation oncologist should also be responsible ultimately for determining the appropriate dose of radiation to be administered.

After the surgeon and radiation oncologist have agreed that the patient is a candidate for radiosurgery treatment, the treatment process may begin. Planning begins when the patient is brought to the CyberKnife treatment suite and positioned on the treatment table. For intracranial lesions a thermoplastic mask is contoured to the calvarium, or the patient is placed on a moldable cradle for extracranial lesions. The patient will then undergo appropriate imaging which always consists of an axial CT scan using 1.25-mm slices. The CT scans are generally done with contrast and a magnetic resonance imaging (MRI) is also frequently useful for intracranial lesions. The addition of myelography or cisternography to the CT scan is often helpful for skull-base lesions and spinal lesions in which there is significant epidural or intradural tumor volume. The data set from these images is imported into the CyberKnife treatment planning station. The treating surgeon pulls up these images and performs the fusion of the MRI to the CT if an MRI was performed. The surgeon demarcates the tumor volume to be treated. This is usually done on the axial planes, but the tumor may also be demarcated in the coronal and sagittal planes. The surgeon will ultimately be responsible for targeting the lesion, and demarcating any surrounding critical structures. At this point a radiosurgical treatment delivery plan is developed with a radiation oncologist and radiation physicist. When this planning process is complete, the patient may be scheduled for radiosurgical dose delivery.

FIGURE 5. Patient being fitted with a thermoplastic mask that provides comfortable restraint during CT scanning and CyberKnife treatment.

On the date of radiosurgical dose delivery, the patient returns to the CyberKnife treatment suite and is repositioned on the treatment couch. The preformed thermoplastic mask or moldable body cradle is placed upon or around the patient as necessary (Fig. 5). Patient positioning begins by treatment staff using an automatic treatment couch to move the patient so that the region of interest is within the x-ray field of view. X-rays are acquired and registered to a library of DRRs constructed before treatment. Translation and rotation of the bony anatomy or implanted fiducials are measured by iteratively changing the position of the anatomy in the DRR until the radiographs and DRRs match. The surgeon is responsible for ensuring that the registration of real-time images and DRRs is accurate (ie, that the treatment site is precisely positioned in the robot's coordinate system), at which point the surgeon allows the treatment to begin. When treatment is initiated, the CyberKnife system determines the initial location of the treatment site and the robot moves the LINAC to this position. The robot then moves the LINAC through a sequence of preset points, or nodes, surrounding the patient along the prescribed path (Fig. 4). At each point at which the robot arm stops, a new pair of real time x-rays may be acquired and the position of the target redetermined. The position is delivered to the robotic arm, which adapts the beam pointing so that patient movements up to 1 cm are compensated for. The LINAC attached to the robotic arm then delivers the preplanned dose of radiation for that beam direction. Larger movements cause the treatment to be stopped so the patient can be repositioned using the automatic couch. This process may be repeated at each node until all planned beams are delivered and the treatment is completed. In practice, it has been found that reimaging at every second, third, or fourth beam results in accurate dose delivery. The treatment is generally completed within 30 to 60 minutes for an intracranial lesion and between 60 and 120 minutes for extracranial lesions. At the completion of the treatment, the patient is released from the CyberKnife treatment couch and can resume normal activities that day.

ECONOMIC FEASIBILITY OF COMPETING RADIOSURGICAL PLATFORMS

Advantages Versus the Gamma Knife

The technological advances that allow the CyberKnife to escape the limitations of frame-based targeting of lesions enable the CyberKnife to treat a variety of lesions outside the cranium and spine. Several clinical series document the growing utilization of the CyberKnife for extra-central nervous system (CNS) lesions[8–10] by non-neurosurgeons. Above and beyond the patient benefits of radiosurgery for these extra-CNS lesions, the capacity of the device is enhanced to a degree that makes the CyberKnife an economically feasible proposition in hospitals that could not otherwise justify an exclusively intracranial radiosurgical platform such as the Gamma Knife. It is likely that extra-CNS pathology will soon account for the predominant share of image-guided full-body radiosurgery procedures. Therefore, a neurosurgeon interested in obtaining access to radiosurgical capabilities for his or her practice no longer has to justify the economics to hospital administrators with a proforma that is limited to the potential patient population in that neurosurgeon's practice or, for that matter, the potential patient population served by all neurosurgeons in the hospital's primary service area. Instead, the hospital administrators can consider for their economic proforma the potential patient population to include all patients with any solid tumor anywhere in the body. The ability to leverage all the volume of oncologic patients across all surgical disciplines should allow every midsize hospital to acquire an image-guided full-body radiosurgical platform. Although in most regions the Gamma Knife has been a technological capability limited to university centers and dedicated entrepreneurial radiosurgical centers and radiosurgical specialists, the economic feasibility of the CyberKnife and its inherent surgeon-friendliness should put radiosurgical capability for CNS lesions in the hands of every neurosurgeon practicing in the civilized world. Just as the once technologically cutting-edge operating microscope and frameless stereotactic surgical navigation systems have moved beyond the initial proving grounds of university medical centers to become commonplace in community neurosurgical practice, treatment planning in the radiosurgical suite will likely become as commonplace for the modern neurosurgeon as a day spent in the operating room.

Advantages Versus Enhanced Radiotherapy Systems

There are multiple radiotherapy platforms that have incorporated technological advances to more precisely localize the delivery of external beam radiation to targeted lesions, including the X-Knife (Radionics, Inc, Burlington, MA), the Novalis (BrainLAB, Heimstetten, Germany), and the Trilogy System (Varian, Inc, Palo Alto, CA). Some of these devices have reportedly achieved a precision in radiation delivery that allows their manufacturers to market the devices as whole-body radiosurgical platforms. There are many differences in these platforms and the CyberKnife, but the chief technological difference for surgeons is that none of these devices as yet allow for continuous imaging and verification of the targeted lesion's location in space. To allow for this potential inadequacy in targeting, treatments are usually fractionated. In contradistinction, the CyberKnife radiosurgeon frequently employs hypofractionation to take advantage of possible radiobiologic benefits of fractionation, not to provide a safety margin for less-than-precise targeting. Indeed, the CyberKnife can be as confidently used for single-session radiosurgery for functional lesions that require submillimetric accuracy, such as trigeminal rhizotomies, as can the Gamma Knife.[11] It would be a challenge for enhanced radiotherapy systems to do the same.

Aside from this paramount technological difference, there is an important economic difference between the CyberKnife and enhanced radiotherapy platforms that neurosurgeons should carefully consider. Because the enhanced radiotherapy systems are just that—enhanced radiotherapy systems—radiation oncologists have a comfort level with the devices that may, in their minds, obviate the need for surgeons in the treatment process. Additionally, the devices can be used for standard fractionated radiotherapy and hypofractionated radiosurgery. Although this capability is a potential economic advantage for the radiation oncologists and the radiation oncology centers that purchase the devices, these capabilities may frequently, if not usually, assign to the involved surgeons, if there are any, a superfluous role in the radiosurgical program. Not only will the involved surgeon have to compete for radiosurgical treatment slots on the device against radiotherapy treatment slots, the surgeon will have to compete for relevance in the entire process, which the radiation oncologist justifiably views as a radiation modality. The surgeon's role in CyberKnife radiosurgery is much different. The CyberKnife, like its forebear, the Gamma Knife, was invented by a surgeon for surgeons as an alternative surgical tool that incorporates the biologic power of focused radiation and the valuable skill set of radiation oncologists. The need for precise anatomic knowledge and localization of the targeted lesion and the potential consequences of delivering large doses of highly focused radiation in 5 or fewer sessions to that lesion essentially dictates the involvement of a qualified surgeon in every CyberKnife or Gamma Knife treatment. This is justifiably not the case with traditional radiotherapy and likely will not be the case with enhanced radiotherapy systems that provide radiosurgical treatments. The definition of radiosurgery has been evolving,[12] but surgeons should insist on one essential and self-evident component of the definition: radiosurgery should always include a surgeon.

Clinical Experience

Intracranial Lesions

Radiosurgery is a well-established treatment for many intracranial lesions, including brain metastases,[13,14] benign tumors near sensitive structures,[15–19] arteriovenous malformations (AVMs),[20,21] and functional disorders such as trigeminal neuralgia.[22,23] The CyberKnife radiosurgical system can be employed for treatment of all lesions that the Gamma Knife can treat, with the flexibility of being able to treat intracranial lesions that are difficult to target with the Gamma Knife such as low skull base tumors and ophthalmologic tumors, and the capacity to easily fractionate treatment of lesions near sensitive structures.

Brain Metastases

Stereotactic radiosurgery is a standard treatment for patients with brain metastases, with well-controlled clinical studies revealing significant survival and palliative benefits in selected patients.[24] In general, CyberKnife treatment of metastatic brain tumors has progressed in a manner similar to Gamma Knife treatment, with single tumors treated in a single, high-dose fraction. Chang et al[25] published early experience with brain metastases in which 72 patients with 84 lesions were treated with single doses ranging from 10 to 36 Gy. The tumor control rate was 95%. Comparable to other radiosurgical devices, a 4% incidence of radiation injury was observed. Shimamoto et al[26] treated 41 patients with 66 lesions using single doses between 9 and 30 Gy. High doses (at least 24 Gy) were more likely to produce freedom from progression than doses of 20 Gy or lower, and were also more likely to eliminate the tumor completely. There were no severe side effects.

An advantage of the CyberKnife versus the Gamma Knife with the treatment of cerebral metastases is that it is very simple to treat more than one lesion with the CyberKnife.[13] Treatment of more than one lesion with the Gamma Knife requires multiple treatment plans and repositioning of the patient in the treatment helmet. In a study by Chang et al,[13] 53 patients with multiple (2 to 5) brain metastases of various histologies were treated with a mean radiation dose of 19.6 Gy. Fifty-two percent of the 132 tumors reviewed on MRI at 3 months posttreatment were smaller (8% had disappeared), 31% were stable, and 9% had increased in size. New metastatic tumors appeared in 12 of the 53 patients within 6 months posttreatment. Median actuarial survival was 9.6 months. Surgery was required for tumor progression and radiation necrosis in a few cases. Overall, a 91% rate of tumor control and a low rate of radiation necrosis were obtained.

Pituitary Tumors

Most pituitary tumors are best treated with surgical resection and medical management. Patients who are poor surgical candidates or who refuse surgical treatment and those with recurrent or residual tumors are reasonable candidates for radiosurgical treatment. The ease of fractionation is a significant advantage of CyberKnife radiosurgery over frame-based Gamma Knife radiosurgery for the treatment of pituitary tumors that compress the optic chiasm. Stanford University Medical School has reported a series of 14 patients with pituitary tumors that were within 2 mm of the optic apparatus[27] (see also Adler et al[28]). Thirteen of the patients exhibited tumor control over a 29-month follow-up. Kajiwara et al[29] treated 21 patients with pituitary adenomas (14 with nonfunctioning and 7 with functioning adenomas). The marginal dose ranged from 6.4 to 27.7 Gy (lower for nonfunctioning adenomas than functioning ones) per fraction. After a nearly 3-year mean follow-up the tumor control rate was 95.2%, and hormone function improved in all the functioning adenomas. Visual acuity worsened in one case due to cystic enlargement of the tumor. Hormonal function improved in all of the 7 functioning adenomas. Hypopituitarism occurred in 2 cases. Staging of the radiosurgical dose delivery may provide a safety margin for the surrounding optic chiasm, and the results of these small series suggest that it does so without a significant decrease in efficacy.

Acoustic Neuroma

There are several large series of patients treated with radiosurgery for acoustic neuroma.[30–32] Across these series 51% of the patients had hearing preserved and greater than 90% retained normal facial nerve function. Hypofractionation of radiosurgery could increase these rates of hearing preservation and enhance radiation sensitivity of the tumor. Stanford University has treated 323 patients with acoustic neuromas with the CyberKnife. Chang et al[3] reported that, of 61 patients treated with 3 daily fractions of 6 or 7 Gy and followed for 3 years, hearing was preserved in 74% and improved in 4%. There was also no progression of acoustic neuroma growth and no permanent facial injuries. In a study of 38 patients with vestibular schwannoma, 14 with serviceable hearing (who received a mean dose of 17 Gy) and 24 without (who received a mean of 16.9 Gy), radiosurgery was delivered in 1 to 3 fractions.[33] Tumor volumes in the hearing patients were much smaller than those in the nonhearing patients, and all lesions were larger than those included in prior radiosurgical studies. The tumor control rate was 94%, and 93% of patients with serviceable hearing before radiosurgery retained this level of hearing. Improved tumor dose homogeneity and fractionated treatment may have been the keys to improved hearing preservation and tumor control in these patients.

Malignant Gliomas

Radiosurgery has a limited role in the treatment of malignant gliomas. Although there has never been a randomized controlled study, there are multiple clinical series that suggest that a radiosurgical boost for appropriately treated malignant gliomas may result in a small increase in patient survival.[34] The flexibility of nonisocentric dose delivery does provide a theoretical advantage of the CyberKnife for treating the usually irregular contours of recurrent malignant gliomas. Unfortunately, these deadly tumors are resistant to established treatment modalities, including stereotactic radiosurgery.

Nasopharyngeal Carcinoma

External beam radiation therapy (XRT) is the primary treatment for nasopharyngeal carcinoma. Relatively high rates of local failure[35,36] have prompted investigation into means of improving treatment, including radiosurgical boost to the treatment area. Improved local control over a mean follow-up of 21 months using a frame-based LINAC[37] led to an investigation of CyberKnife boost treatment of nasopharyngeal carcinoma at Stanford University.[38] They treated 45 patients with boost radiosurgery after standard XRT administered to a total dose (in most patients) of 66 Gy in 2-Gy daily treatments. Patients were treated with radiosurgery within 4 weeks of XRT, using one fraction of 7 to 15 Gy. After a mean follow-up of 31 months there were no local recurrences. The 3-year local control rate was 100%, the rate of freedom from distant metastasis was 69%, the progression-free survival rate was 71% and overall survival was 75%. The benefit of CyberKnife radiosurgery in these cases includes the advantage of being far less invasive than the common alternative of local brachytherapy.

Meningiomas and Perioptic Tumors

The ability to conveniently fractionate radiosurgical dose delivery, potentially leading to enhanced safety and efficacy in pituitary and acoustic tumors, may also improve the treatment of perioptic tumors. This ability has led CyberKnife users to treat lesions that were previously not considered treatable using other radiosurgical treatment systems. In the first report of CyberKnife radiosurgery for these lesions, Mehta et al[39] treated 13 patients with lesions near the anterior visual pathways. Treatment planning was based on fused CT and MR images. Patients received a total of 20 to 25 Gy delivered in 2 to 5 fractions prescribed to the 75% to 95% isodose line. Treatment plans kept the volume of optic nerve that received appreciable levels of radiation to a strict minimum. At a median follow-up of 18 months local tumor control was 100%, 4 patients had improved vision, and none showed visual deterioration.

This small feasibility study led to the more extensive report of Pham et al.[27] In this series, 34 patients with either meningiomas or pituitary adenomas within 2 mm of the anterior visual pathways received 2 to 5 sessions of radiosurgery separated by at least 24 hours. After a mean follow-up period of 29 months (range, 15 to 62 mo), 32 patients (94%) experienced either a decrease or stabilization in tumor size. Although there was no change in visual field or acuity in 20 patients, improvement in vision was documented in 10 cases. Three patients experienced visual loss secondary to optic nerve damage; tumor progression was the cause in 2 cases. A more recent follow-up to this report[28] was equally promising, with excellent tumor control and visual field or acuity preservation in 94% of patients. It is believed that the safety and efficacy of CyberKnife radiosurgery in these cases depends critically on precise targeting and fractionated treatment.

Trigeminal Neuralgia

The Gamma Knife was conceived by Leksell for the purpose of treating trigeminal neuralgia, and clinical trials attest to its efficacy in such cases.[40–42] There are several CyberKnife-specific clinical series reporting results of radiosurgical rhizotomy.[11,23,43] A multi-institutional study included 41 patients treated for idiopathic trigeminal neuralgia.[11] The targeted area was the retro-gasserian region of the trigeminal nerve, which was treated with 60 to 70 Gy prescribed to the 80% isodose line. Median latency of pain relief after single-session radiosurgery was 7 days. Pain control was ranked as excellent in 36 patients (87.8%), moderate in 2 (4.9%), and unchanged in 3 patients. Six (15.8%) patients with initial relief experienced recurrence in a range of 2 to 8 months. Long-term pain control (mean follow-up of 11 mo) was obtained in 78% of the patients. Twenty-one patients (51.2%) experienced numbness after treatment. The latency to pain control was often considerably shorter than after comparable Gamma Knife treatment, a fact that may reflect the ability of the CyberKnife to target radiation nonisocentrically along the length of the treated nerve. Similar outcomes were reported more recently in a paper showing improved visualization using CT iohexol cisternography to identify the 6 to 8-mm segment of nerve to be lesioned.[23]

CyberKnife Radiosurgery in Children

Radiosurgery has considerable theoretical value in the treatment of children because of the special sensitivity of the developing brain to radiotherapy.[44,45] Unfortunately, radiosurgery in children has been limited due to the difficulty of applying a skull frame to children. Giller et al[45] reported on 38 radiosurgical procedures in 21 children with tumors of varying pathology. The mean target volume was 10.7 cm^3 treated with a mean marginal dose of 18.8 Gy. Local control was achieved in cases of pilocytic and anaplastic astrocytoma, medulloblastoma, and craniopharyngioma, but ependymomas in 3 children did not respond. There have been no procedure-related deaths or complications. Although the delivery of CyberKnife radiosurgery in children is painless and a small amount of patient motion can be compensated for by the image guidance system, the authors suggest that it is generally preferable to provide some type of heavy sedation or general anesthetic for delivery of radiosurgery to young children using a CyberKnife. Older children can frequently be cooperative enough to undergo CyberKnife radiosurgery without sedation or anesthesia. CyberKnife radiosurgery has also been shown to be safe and feasible, and in selected cases effective, in infants.[44]

Spinal Tumors and Vascular Malformations

The CyberKnife allows the well-established efficacy of intracranial radiosurgical techniques to be extended to lesions in the spine. Although targeting of intracranial lesions has always been based on anatomic features of the skull, until recently targeting of spinal lesions has been based on implanted radiopaque fiducial markers.[46,47] The introduction of a spine tracking system (Xsight, Accuray, Inc) has eliminated the need for fiducial implantation for most spinal treatments, thus increasing patient comfort and decreasing the time between initial patient evaluation and treatment. Recent end-to-end tests of accuracy using lifelike phantoms have revealed total clinical accuracy of this spine-tracking system to be <1 mm.[48,49]

General radiosurgical dosing parameters for spinal tumors have been based on prior experience with intracranial radiosurgery for similar pathologies.

There is essentially no literature on dose tolerances for radiosurgical delivery to the spine. Working limits are established by parameters for spinal cord radiation dose limits of fractionated radiation therapy. These, in turn, are generally based on empirical clinical observation and animal data. The risk of myelopathy is 1% for radiation regimens of 4500 cGy delivered in 22 to 25 fractions, and this has constituted a commonly accepted dose limit.[50] The dosing guidelines for spinal radiosurgery are much less clear, but Chang indicates[51] that, as a general guideline, the dose and staging of radiosurgery for spinal lesions should rest between those used for conventional fractionated radiation therapy for the spine and the radiosurgical dose used to treat similar pathology in the brain. In general practice, a dose limit of 800 cGy to the spine is considered acceptable.

Stanford University has compiled a large series of spinal lesions treated with CyberKnife radiosurgery. The dosage used in their reported series would generally range 20 to 21 Gy in 2 to 3 stages for lesions within the spinal canal or within the spinal cord itself. Bony metastases were treated with a single dose of 16 Gy or 20 Gy divided over 2 stages. Of the 123 patients reported, only 2 developed radiographic and clinical evidence of spinal cord myelitis. Of the 123 patients, 51 had intradural-extramedullary benign spinal tumors for a total of 55 lesions. Of those benign lesions, the majority had pain at presentation. Approximately 70% of those patients with meningiomas and 50% of those patients with schwannoma who had pain reported a significant reduction in pain at 12 months after the radiosurgical treatment. Of the 7 patients with neurofibromatosis with pain, none had improvement in their pain. Among all patients with benign tumors, 4 lesions enlarged slightly, 2 of these later regressed on subsequent MRIs and 2 of those patients underwent surgical removal to address myelopathy.

In many centers CyberKnife radiosurgery is used to treat spinal metastases. The largest series is from the University of Pittsburgh, who presented outcomes from 115 patients, including 108 metastatic lesions.[52] This group treats exclusively using a single-fraction technique in which 12 to 20 Gy (mean, 14 Gy) was prescribed to the 80% isodose line. No acute radiation toxicity or new neurologic deficits occurred during the follow-up period (median, 18 mo). Axial and radicular pain improved in 74 of 79 patients. In another series, 50 patients with 68 spinal breast metastases were treated.[53] Seventy-one percent of the lesions had been previously irradiated. Most tumors were treated with 19 Gy in a single fraction. In 48 cases, a significant decrease in pain was observed during the follow-up period of 6 to 48 months (median, 16 mo). Local control was achieved in 8 asymptomatic lesions treated as primary therapy. Further clinical studies in Pittsburgh focused on radiosurgery for spinal renal-cell metastases[54] and melanoma,[55] with equally good results. This group also recently combined radiosurgery with kyphoplasty fixation of the spine.[56] The novel combination of 2 minimally invasive procedures to stabilize spine fractures and control tumor growth has the potential to greatly ease the course of effective treatment for this group of patients.

A factor influencing the local control rate is the presence of previous irradiation; among the 51 patients treated at the Georgetown University Hospital for various metastatic lesions[57] a local control rate of 100% was achieved on the patients who had not been previously irradiated, but there were 3 recurrences among the patients who had undergone irradiation before radiosurgery. Only minor and transient side effects of radiosurgery were observed during a 3-month follow-up period. The authors also found that CyberKnife radiosurgery improved pain control and maintained pretreatment quality of life.

Dodd et al[58] published their experience treating 55 benign spinal tumors with CyberKnife radiosurgery. Lesions ranging in volume from 0.136 to 24.6 cm^3 were treated in 1 to 5 fractions with 16 to 30 Gy to an average 80% isodose line. Doses varied depending on histology, from a mean of 2031 cGy for spinal meningiomas to 1870 cGy for spinal schwannomas. Pain was reduced in 25% to 50% of patients (depending on histology) 12 months after CyberKnife radiosurgery (over half the patients had greater than 24 mo follow-up). All lesions were either stable (61%) or smaller (39%). Radiation-induced myelopathy occurred 8 months after radiosurgery in 1 patient.

Intramedullary spinal cord AVMs (SCAVMs) are rarely amenable to traditional endovascular embolization and microsurgical resection because these modalities pose too great a risk to the spinal cord. Spinal radiosurgery could be an important therapeutic tool in patients with SCAVMs. A study of 21 patients with intramedullary SCAVMs (11 cervical, 7 thoracic, and 3 lumbar) treated at Stanford University was recently published.[59] Radiosurgery was delivered in 1 to 5 sessions to an average AVM volume of 1.8 cm^3 (range: 0.14 to 4.94 cm^3) using an average marginal dose of 19.5 Gy (range: 15.0 to 21.1 Gy). After a mean clinical follow-up of 29 months (range, 3 to 93 mo), 6 patients have been studied with posttreatment angiography; AVM obliteration was partial in 4 and complete in 2 patients. Significant AVM obliteration was observed on MRI in most cases at a 1-year follow-up. No patient experienced a postradiosurgical hemorrhage.

CONCLUSIONS

CyberKnife radiosurgery represents a significant advance over the very successful Gamma Knife radiosurgical treatment platform. Because of its technologically advanced way of localizing the tumor and delivering the radiation, CyberKnife radiosurgery does not require a stereotactic frame attached to the skull and does not have to deliver radiation in an isocentric dose distribution. These advances allow the CyberKnife radiosurgical platform to be used with greater flexibility for intracranial lesions, allow for easy fractionation of radiosurgical delivery, and provide the opportunity for radiosurgical treatment of lesions outside of the cranium to include a broad array of spinal pathology. The application of radiosurgery to the treatment of spinal lesions is likely to provide the same revolutionary advance in treatment of spinal lesions as occurred with the treatment of intracranial lesions at the introduction of the Gamma Knife. All neurosurgeons would be well-served to understand this technology and its application to neurosurgical disorders.

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