Chapter 28
Emerging Indications in Stereotactic Radiosurgery: The First Application of Cellular Surgery

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At this meeting of the Congress of Neurological Surgeons, the theme "Surgery at the Crossroads" was presented. Stereotactic radiosurgery reflects one important neurosurgical field that crosses the lines of multiple medical disciplines. To discuss the role of radiosurgery and its emerging indications in this context, it is important to first define surgery.

We defined surgery as "definitive manipulation of an organ system or tissue to achieve a specific purpose, performed in a single-session, using energy." (19) Historically, the most common energy source was mechanical. The surgeon simply moved his or her arm that held an instrument. Over the years, other forms of energy were used as a surgical effector. These included light energy (laser surgery), thermal energy (radiofrequency lesioning), chemical energy (tissue manipulation with alcohol or chymopapain), and radiation energy (stereotactic radiosurgery).

For decades, one focus of neurosurgery residency training has been to master microneurosurgical techniques using exposure augmented by the operating microscope. Radiosurgery represents the first way to truly perform microsurgery, that is, surgery on a submicroscopic level. Radiosurgery is the first surgery for disruption of tumor-cell membranes, surgery to disrupt the strands of DNA, surgery to eliminate protein biosynthesis, and surgery of endothelial cells. Radiosurgery truly has become the first broadly applied biologic surgery. Thus, it is important to evaluate its current and emerging uses and identify how surgeons will use this tool for the spectrum of disorders that they manage (28). Previously, newly emerging radiosurgical indications had their roots in our understanding of radiobiologic effects on different tissues. To date, radiosurgery has been used for both abnormal intracranial mass lesions and normal brain. Table 28.1 shows the current brain radiosurgery experience at the University of Pittsburgh.

RADIOBIOLOGY AND THE BASIS OF THE RADIOSURGERY

Borje Larsson, a radiobiologist working with Lars Leksell, performed the first basic science experiments in radiosurgery using protons and then photons. Their goal was to create small brain lesions in the hope of improving the care of patients with functional disorders. Subsequent animal studies in rabbits, cats, goats, rats, and later subhuman primates showed consistent effects on small-volume lesions using high radiation doses. A baboon model pioneered at the University of Pittsburgh studied effects between 1 and 24 months using maximum doses of 20, 50, 100, and 150 Gray and 8-mm collimators (17). Imaging studies identified the time course for lesion development and the resolution of imaging changes that followed (28). Histologic studies proved that the lesion was created sharply with a rapid follow-up of the histologic effect outside the lesion. The 50 Gray dose, more typically used in human clinical radiosurgery for arteriovenous malformations, was followed by complete target destruction if enough time elapsed. This indicated that arteriovenous malformation (AVM) obliteration could not only occur from a selective effect on the vessel wall, but also from total tissue destruction at the target. Such studies raised the hope for the use of radiosurgery in vascular malformations, neoplasms, and other functional targets such as tremor cells, pain pathways, and perhaps epileptic foci.

"NORMAL" BRAIN AS THE TARGET

The most common functional indication is trigeminal neuralgia (3, 15, 16). The effects of trigeminal nerve radiosurgery have been evaluated in a subhuman primate model. Using maximum radiosurgery doses of 80 or 100 Gray, Kondziolka et al. (18) studied histologic and ultrastructural effects on the nerve target 6 months after irradiation. They found evidence of axonal degeneration at the 80-Gray human dose that was not specific to different kinds of nerve fibers. The 80-Gray dose led to a subtotal axonal degeneration with preservation of some axons. This indicated that the high rate of facial sensory preservation was because of the fact that the lesion was not complete, and pain relief likely occurred from degeneration of enough axons that blocked pain.

Baboon studies using 100 or 150 Gray in the thalamus provided additional basis for the use of radiosurgery to create thalamotomy lesions in patients with movement disorders (11). To date, radiosurgical thalamotomy has been used in patients with tremors related to Parkinson's disease, essential tremor, and multiple sclerosis tremor (17). Published reports indicate that the rate of significant improvement is approximately 80% using maximum doses of 130 to 150 Gray with a single 4-mm collimator, targeted to the ventral intermediate nucleus (VIM) of the thalamus. High-resolution, stereotactic magnetic resonance imaging is crucial for targeting. For the most part, radiosurgical thalamotomy is used in patients who are elderly or medically infirm and who do not want to undergo deep brain stimulation with placement of hardware or radiofrequency thalamotomy.

Radiosurgery for epilepsy has been used in increasing numbers of patients with a variety of different brain targets. The basis for the use of radiosurgery was the observation that irradiation could stop seizures in patients with brain tumors or vascular malformations (23). Animal studies (rat kainic acid or rat kindling models) showed a reduction or elimination of seizures after radiosurgery (25). Dr. Nicholas Barbaro and colleagues at the University of California at San Francisco conducted a multicenter study to evaluate the effects of radiosurgery for mesial temporal sclerosis-related epilepsy. Patients were randomized to maximum doses of 40 or 48 Gray using target volumes between 5.5 and 7.5 mL. This work followed the pioneering efforts of Regis et al. (30), who first studied mesial temporal lobe sclerosis-related epilepsy in Marseille, France. Radiosurgery for hypothalamic hamartoma-related gelastic seizures is an important therapeutic alternative to hamartoma resection or to radiofrequency lesioning (30).

An additional emerging indication is anterior capsulotomy for obsessive-compulsive disorder. Radiosurgical lesioning has been performed for depression (cingulotomy), chronic pain (medial thalamotomy), cancer pain (hypophysectomy) and other anxiety neuroses but requires additional research before any of these indications becomes more mainstream.

"MALFORMED" BRAIN AS THE TARGET

For several decades, perhaps the most frequent radiosurgical indication was the AVM (5, 23). When an AVM was located in a region of the brain associated with high risk for surgical resection, radiosurgery often was considered as the main therapeutic alternative. Particularly in patients with smaller-volume, critically located malformations, radiosurgery has proven a highly effective strategy. The various management options including conservative therapy, endovascular embolization, resection, and radiosurgery (sometimes alone or in combination) should be discussed with symptomatic patients. Larger-volume AVMs are occasionally selected for radiosurgery, usually using a staged-volume approach (1), when no other option is feasible. Patients with dural arteriovenous fistulas may also be appropriate candidates for radiosurgery, sometimes followed by endovascular or open surgical approaches (37).

Cerebral cavernous malformations are an emerging radiosurgical indication in patients with deep-seated lesions unsuitable for microsurgery. This common malformation, easily identified on magnetic resonance imaging scans, presents an ideal radiosurgical target for a number of reasons. First, these lesions usually are small and located in critical brain areas. Most patients have minimal symptoms, and natural history studies show a relatively infrequent annual hemorrhage rate in patients without previous symptomatic hemorrhage (0.6% per year). Only in patients with significant single hemorrhages or multiple hemorrhages should radiosurgery be considered. The University of Pittsburgh protocol initially included only patients with two imaging-defined symptomatic bleeding episodes in locations at high risk for neurologic deficits with resection. To date, we have performed radiosurgery on 112 patients whose median age was 39 years (10). The mean margin dose to the malformation was 16 Gray and the maximum dose 30 Gray. The mean number of previous symptomatic bleeding episodes was 2.6. After radiosurgery, at an average of 5 years, the 40% annual hemorrhage rate before radiosurgery (excluding the first hemorrhage) was reduced to 9.7% within 2 years and 0.56% after 2 years.

Thus, radiosurgery may transform a malformation with a propensity to repeated symptomatic hemorrhage into one that is quiescent. Whether or not the lesion is truly obliterated completely cannot be determined using available imaging methods.

NEOPLASTIC BRAIN AS THE TARGET

There has been extensive experience in the use of stereotactic radiosurgery for patients with a wide array of benign and malignant brain tumors. Such work is based on the known radiobiologic effects of radiation on neoplastic tissue. Stereotactic precision and the overwhelming biologically effective single-procedure dose (compared with standard radiotherapy) have led to impressive results after tumor radiosurgery. Animal models, particularly using glial tumors in rat brain, have shown the benefits of focused radiation in comparison to animals that were not radiated. Additional research has been performed using human schwannoma and meningioma xenografts implanted into the sub-renal capsule of nude mice. Recently, we measured tumor apoptosis after radiosurgery in rats with malignant tumors (39). In an analysis of apoptosis performed in the immediate postirradiation period, the number of apoptotic bodies increased significantly compared with controls. Thus, the acute affects of radiation may not only be mediated through delayed tumor cell necrosis but by apoptotic pathways.

Such work on the biologic effects of radiosurgery is the foundation for the observations seen in many thousands of patients managed with intracranial tumors. The most frequent benign tumor cared for by radiosurgery is the vestibular schwannoma (acoustic neuroma). Numerous studies have shown not only excellent short-term outcomes, but also consistent long-term effects now published with 15-year follow-up data (20). Kondziolka et al. (14) reported 5- to 10-year outcomes including information on patient-reported complications and satisfaction rates. Regis et al. (30) compared cohorts of patients who either underwent gamma-knife radiosurgery or microsurgical resection for their vestibular schwannoma. In that study, clinical outcomes were superior in the radiosurgery group. At the same time, imaging studies from numerous centers have clarified what can be expected after radiosurgery. Loss of central contrast enhancement followed by slow progressive tumor shrinkage is most frequently observed. In some patients, transient expansion of the tumor capsule (usually by 1 or 2 mm) can be seen if the internal biologic effect is pronounced. Such tumors later regress in most instances. Imaging studies that show tumoral compression of the lateral brain stem surface may show regression completely off the brain stem over several years. In an earlier report from our center, we noted that over 70% of tumors were smaller once 5 years of follow-up had passed (14). The combination of high tumor control rates and low cranial neuropathy rates (less than 1% for facial weakness and less than 3% for facial numbness, as well as high rates of hearing preservation) have led to the emergence of radiosurgery as possibly the most frequent treatment choice for patients with vestibular schwannomas (24, 28). Other cranial nerve schwannomas are also appropriate for radiosurgery (29).

Similar outcomes have been reported in patients with meningiomas, either managed primarily or after previous surgical resection (13). Radiosurgery has played its largest role in tumors of the skull base and those located close to dural sinuses or cranial nerves (6, 22). High tumor control rates (more than 90%) past 10 years of follow-up have been noted in evaluated patients, again with infrequent rates of associated cranial neuropathy when proper patient selection and judicious dose planning was performed. Another dural based tumor, the hemangiopericytoma, can respond dramatically to radiosurgery, and often marked tumor regression is noted on follow-up imaging studies (36).

Radiosurgery in children is an under-used management approach. When it would be desirable to restrict radiation administration to much of the developing brain (as could be achieved in radiosurgery), this approach should be considered. Perhaps the most common indication in children is management of the recurrent or residual pilocytic astrocytoma located in a deep-brain location (4). Radiosurgery is usually performed under general anesthesia in patients younger than 12 years old. In more than half of the patients managed, significant reduction in tumor size was noted after pilocytic astrocytoma radiosurgery. Radiosurgery has also played a significant role in patients with small residual or recurrent solid craniopharyngiomas, ependymomas, medulloblastomas, and germ cell neoplasms (7, 9). Extracranial radiosurgery for tumors of the nasopharynx or skull base has proven effective for patients with recurrent tumors, particularly after previous resection or radiation therapy (2).

Care of the patient with brain metastases has emerged as the most frequent indication for stereotactic radiosurgery (8, 21, 31–33, 35). It is believed that there may be more than 300,000 patients per year in the United States who develop a brain metastasis from systemic solid cancers. First, radiosurgery was evaluated in patients with solitary metastasis. Now, it has proven to be effective for patients with more than one metastasis. We routinely offer this approach for patients with up to eight tumors who remain in good neurologic condition and remain actively managed for their extracranial disease. Most such tumors are not associated with the significant mass effect that might cause marked neurologic disability. In such patients, surgical resection should be considered if appropriate based on brain location.

The role of whole-brain radiation therapy remains controversial for patients with limited numbers of brain tumors but remains an important strategy for patients with multiple metastases, particularly in the setting of metastatic lung or breast cancer. In tumors that are often considered more “radioresistant,” such as melanoma or renal cell carcinoma, radiosurgery alone may be performed (32). Median survivals after radiosurgery have been noted in patients with lung cancer (11 mo), renal cell cancer (11 mo), breast cancer (13 mo), melanoma (7 mo), and gastrointestinal tract cancer (5 mo) after radiosurgery. Such outcomes vary depending on what can be offered for concomitant management of extracranial cancer. For example, it is infrequent that a patient with a gastrointestinal primary would develop a brain tumor without additional lung or liver metastases.

Other tumors suitable for radiosurgery include chordomas and chondrosarcomas (26), craniopharyngiomas, glomus tumors (34), hemangioblastomas, and pituitary adenomas. There are numerous reports on all of these indications that discuss the role of adjuvant or primary radiosurgery for properly selected patients. Radiosurgery can also play an important role for patients with malignant glial neoplasms, either as a boost to fractionated radiotherapy or for later recurrence (12, 27). It should be considered within a multi-modality strategy for these difficult tumors.

TABLE 28.1. Gamma-knife radiosurgery at the University of Pittsburgh 1987–2005

(n = 7018)[a]

Indication	No. of procedures
Arteriovenous malformation	1047
Cavernous malformation	119
AV fistula	21
Vestibular schwannoma	1075
Trigeminal schwannoma	36
Jugular foramen schwannoma	27
Other schwannoma	13
Meningioma	990
Pituitary adenoma	232
Craniopharyngioma	47
Chordoma	26
Chondrosarcoma	17
Hemangioblastoma	37
Pineal region tumor	25
Hemangiopericytoma	27

Hemangioma		7
Choroid plexus papilloma	7	
Lymphoma		10
Glomus tumor		
Glioblastoma multiforme	277	
Anaplastic astrocytoma	112	
Astrocytoma/oligodendroglioma	105	
Ependymoma		52
Medulloblastoma	19	
Brain metastasis	1902	
Other tumor		37
Skull base malignant tumors		28
Trigeminal neuralgia		625
Thalamotomy for tremor	57	
Epilepsy	6	
Capsulotomy for OCD	1	
Ablation for cancer pain	2	

[a]AV, arteriovenous.

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