Stereotactic Radiosurgery: Instrumentation and Theoretical Aspects—Part 1

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Abstract

In the five decades since its introduction as a concept, radiosurgery has been technically refined to the point where it has revolutionized many aspects of treating central nervous system disease.

This article reviews the technical basis of stereotactic radiosurgery as well as the radiobiologic principles underlying its use.

Introduction

In the past 15 years, radiosurgery has emerged as a cornerstone of treatment for a number of benign and malignant diseases of the central nervous system. Since the 1950s, when Lars Leksell pioneered its development, radiosurgery has been continually refined with the advent of modern imaging techniques and computer-controlled dosimetry. Recently, radiosurgery has revolutionized treatment of benign lesions of both the central nervous system and its supporting structures and offers new hope to people diagnosed with malignant disease of the brain and spinal cord.

Modern radiosurgery methods depend on precision radiation delivery devices, high-resolution three-dimensional imaging techniques, high-performance desktop computing, and experientially developed dose selection. Substantial changes in these factors over the past two decades have resulted in clinically significant improvement in tumor control and side effect profile.

In this combined literature review and technology assessment, we describe the history of the radiosurgery concept, its technological basis, and radiobiological principles.

Radiosurgery: The Concept and Its Development

In 1951, Swedish neurosurgeon Lars Leksell introduced the concept of stereotactic radiosurgery (SRS).[1] Leksell's initial efforts were directed toward developing a method for using noninvasive lesioning in functional neurosurgery. These efforts used an orthovoltage x-ray tube attached to a stereotactic frame to produce converging beams which intersected at the treatment target. Further development of the concept culminated in the 1968 clinical introduction of the first gamma knife unit (in Stockholm).

In classical radiosurgery as developed by Leksell, delivery of radiation energy is highly conformal: Radiation energy is focused so that the treatment volume receives a high, therapeutic prescription dose while surrounding normal tissue is given a relatively low dose. Typically, to achieve this dose, intersecting beams of radiation are cross-fired at a single target. The distribution of radiation energy can be tailored by precisely following the margins of the treatment volume so that rapid dissipation of dose beyond those margins spares normal tissue. Another characteristic of classical radiosurgery is that the radiation dose is given in a single session, whereas now-conventional radiation techniques deliver multiple small doses over an extended period (days or weeks). Conventional radiation techniques thus take advantage of radiobiological differences between tumor and normal tissue, whereas all tissue treated by single-fraction radiosurgery receives the same dose and thus is affected equally.

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In this way, radiosurgery differs fundamentally from conventional radiotherapy. Relatively nonconformal radiotherapy uses fractionation to affect tumor and normal tissue differentially. Radiosurgery seeks to conform a radiation dose spatially to achieve the same means. This precision in three-dimensional dose

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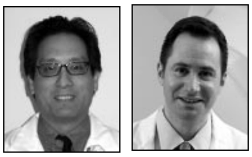

distribution has been described as knifelike, thereby justifying the concept of this treatment as a surgical procedure.

Recent advances in instrumentation have led to development of purpose-built devices to combine radiosurgery (a high-conformity treatment) with dose fractionation as used in conventional radiotherapy. Such treatment has been called fractionated stereotactic radiotherapy (abbreviated as FSR or SRT) and is an exciting development that has made feasible the treatment of lesions not addressable by either classical radiosurgery or conventional radiotherapy.

Technical Aspects

Since the introduction of the gamma knife, several newer implementations of photon radiosurgical devices have been developed. These include a number of linear accelerator-based devices, including X-Knife (Radionics, Burlingame, MA), Novalis (BrainLab, Helmstetten, Germany), and CyberKnife (Accuray, Sunnyvale, CA). In addition to the photon-based devices, charged-particle radiosurgery using the Bragg peak phenomenon represents an alternative technology. Regardless of the underlying technology, however, all of these devices were developed for the same purpose: delivery of highly conformal radiation energy. Each device has its relative merits and implications for dose planning and treatment.

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Gamma Unit (Gamma Knife)

The Leksell Gamma Unit is both the simplest and the oldest currently used device. As such, its capabilities and results are well known. Current units use 201 cobalt-60 sources enclosed within a hemispheric vault. The radioactive decay of cobalt leads to emission of gamma ray energy that is then directed through precisely machined portals so as to converge at a single target. The mechanical simplicity of the gamma knife allows high-precision treatment of lesions and functional targets. Because of the fixed aperture of the collimators, multiple spherical "shots" must be combined to yield conformal treatment of a lesion. This technique allows for shaping highly conformal treatments, but this effect is achieved at the cost of generating "hot spots"—sometimes as high as twice the marginal prescription dose—within the treatment volume. The hemispheric configuration of the gamma knife limits its use to intracranial targets, and treatment is largely limited to single-fraction radiosurgery applications.

LINAC Radiosurgery

Linear accelerator radiosurgery was introduced in the early 1980s by customizing general-purpose linear accelerators used for conventional external beam radiotherapy so as to obtain high-conformity treatment.[2-6] These devices use a magnetron to accelerate electrons that then collide with a target to generate photons. These photons are then focused through a portal to achieve a collimated beam of gamma radiation. The linear accelerator is mounted to a gantry that can rotate through an arc, thereby concentrating radiation energy at a target. By using multiple intersecting arcs coupled with differential beam weighting, high conformity can be achieved.

Until recently, use of these devices was cumbersome in comparison with gamma units and therefore resulted in laborious planning and treatment. However, recent innovations in LINAC technology have radically simplified this planning and treatment such that overall throughput is comparable to that enabled by the gamma knife device. In addition, the physical characteristics of linear accelerator devices allow this technology to be used for treating extracranial targets. Because relocatable frames can be used with these devices, fractionated stereotactic radiotherapy treatments can be delivered.

Current devices using linear accelerator sources include Novalis (BrainLab, Helmstetten, Germany), Peacock (Nomos, Cranberry, PA), X-Knife (Radionics, Burlington, MA), Trilogy (Varian Medical Systems, Palo Alto, CA), and CyberKnife (Accuray, Sunnyvale, CA). These new-generation devices allow greater flexibility of treatment while maintaining high accuracy and precision comparable to the gamma knife. Because of the mechanical complexity of these devices, however, strict daily quality control measures must be applied to every aspect of the operation of these devices.

Proton Beam Radiosurgery

Particle beam radiation therapy has been investigated since the 1940s,[7] and Lars Leksell studied this technique before development of the gamma knife.[8] The differences in biological effectiveness in tissue between proton radiotherapy and conventional linear accelerator or gamma knife-based treatment are minimal. The key to the concept of particle radiosurgery is use of the Bragg Peak phenomenon. While rapidly traveling through tissue, high-energy proton beams lose energy. As this energy is lost, the likelihood of the particle interacting with the tissue increases. This leads to deposition of most of the energy within a discrete band of spatial depth measuring roughly 12-16 mm. The Bragg peak itself is generally not sufficient to develop conformal treatments without multiple superimposed and intersecting beams. Carefully developed plans can theoretically result in higher conformities than are possible using photon-based techniques.

Although the theoretical advantages of proton-beam radiosurgery are clear, no evidence thus far exists that has shown superiority of this technique in the clinical setting over photon-based techniques, either from the standpoint of disease control or toxicity. Results using this modality for acoustic neuromas and arteriovenous malformations failed to show superiority over conventional radiosurgery.[9,10] In addition, implementation of these devices is poorly standardized, and the paucity of reliable data from the few centers using these devices complicates any comparison of results with either LINAC or Gamma Unit radiosurgery. The few data that do exist, however, have suggested a higher rate of complications and a lower tumor control rate than is achievable with either photon-based devices.

Biological Aspects

The radiation doses prescribed for conventional radiotherapy treatments have developed from decades of clinical experience. Early in the era of clinical radiotherapy, researchers realized that the use of multiple treatments (called fractions) with reduced doses per fraction improved the therapeutic ratio when treating both benign and malignant tumors. Radiobiological principles developed subsequently helped to explain the increase in therapeutic ratio gained from multiple treatments. An important biological rationale for improving the therapeutic ratio of radiotherapy is repair of normal late-responding tissue between each fraction of radiation delivered. Compared with tumor tissue, tate-responding tissue with slow cell turnover (eg, central nervous system tissue) has a higher capacity for repairing the sublethal damage caused by radiation. However, tumor tissue does have some capacity for repairing small amounts of sublethal damage between each fraction of radiation, and this activity competes against the desired killing of tumor cells. The benefit of multifraction radiotherapy is gained by treatment designs that balance increases in killed tumor cells associated with minimizing tumor cell repair and tumor cell repopulation between each treatment. To maximize the therapeutic ratio, the dose per fraction and time interval between each fraction must also be planned in such a way that late-responding normal tissue (eg, central nervous system tissue) is given adequate time to repair the sublethal damage. Also competing against tumor cell killing are the areas of hypoxia within the tumor mass. These hypoxic cells are threefold less sensitive to radiation damage than oxygenated cells.[11] Reoxygenation of hypoxic areas can occur between each fraction of radiation as oxygenated cells around the periphery of the tumor are eradicated.[11] This reoxygenation allows areas of hypoxia to gain closer proximity to oxygenated areas. Treatment with multiple fractions over time also allows reassortment of cells into more sensitive phases of the cell cycle. These basic principles of radiation biology have been traditionally referred to as the four "R's: repair, repopulation, reoxygenation, and reassortment.

The radiobiologic principles, which govern the design of conventional radiotherapy multifraction treatments, do not necessarily apply to single-fraction, high-dose stereotactic radiosurgery. The difference between single-fraction stereotactic radiosurgey and conventional fractionated radiotherapy is that the goal of radiosurgery is to obliterate a predefined target volume. Conventional fractionated radiotherapy must use a dose prescription below the tolerance of normal tissue in the volume treated so as to purposely include a "margin" of normal tissue around the target lesion to account for daily setup error or subclinical disease. Stereotactic radiosurgery allows precise delivery of a single high-radiation dose to a defined target volume and rapid dose falloff outside this volume. Normal tissue is purposely excluded from the target volume as much as possible; thus, repair of normal tissue during the treatment is of little concern in stereotactic radiosurgery. During a single-fraction treatment, reoxygenation and reassortment in the classic sense do not occur.[12] Therefore, according to classical radiobiology, stereotactic radiosurgery should be less effective for metastatic tumors of the central nervous system. However, the medical literature has repeatedly disproved this supposition.[13] In general, stereotactic radiosurgery is more effective for control of metastatic lesions, especially the histologic types classically believed to be radioresistant. The current assumption is that single high-dose treatment overcomes the radioresistance of hypoxic cells as well as cells in the less-sensitive phase of the cell cycle. Another important observation to consider is that classic ra-

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diobiologic principles to not account for the gliosis and proliferative vasculopathy which occur from radiosurgical treatment. These and other events may also account for the enhanced biologic effectiveness of single-fraction treatment.[14]

A newer approach developed in recent years is use of fractionated stereotactic radiotherapy (FSR). This treatment allows use of the same precision techniques as stereotactic radiosurgery but improves the therapeutic ratio for treatment in eloquent areas of the brain through use of multiple fraction treatments. A mathematical model has been devised to describe the therapeutic gain for fractionated stereotactic radiotherapy versus single-fraction treatment.[15] An increase in the therapeutic gain is seen when progressing from 1 to 10 fractions and is seen only incrementally beyond ten fractions. The developers concluded that increasing the "margin" of normal tissue around the target for daily setup error reduced potential biological gains.[14] FSR has been shown to be an important tool for treatment of tumors: The technique approximates structures known to have tolerance below that of brain parenchyma (eg, the optic chiasm).[16] By the use of multiple fractions, the total treatment dose can be kept below the radiation tolerance of this structure while still achieving effective tumor control. Fractionated stereotactic radiotherapy has traditionally been confined to use of modified linear accelerators and generally is not compatible with a gamma knife system. In recent years, the technique has been improved by development of more precise relocatable frame systems.

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Conclusion

Representing a complex technical achievement in modern medicine, contemporary radiosurgery has a long history and is based on rigorously defined radiobiological principles. Modern practitioners of radiosurgery have at their disposal a variety of different devices and treatment strategies. Clinical results and indications are discussed in Part 2 to this manuscript, which will appear in the Spring 2006 issue. ❖

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