Leksell Gamma Knife Radiosurgery

Diogo P. Cordeiro and David J. Schlesinger

Introduction

Since Lars Leksell's conceptual invention of radiosurgery in 1951 [1], the fundamental principle of radiosurgery has always been to focus energy within a targeted lesion while minimizing injury to surrounding tissue. Leksell and his collaborators were able to create practical connections among several different lines of thinking in order to eliminate the barriers to actualizing this vision: stereotaxy to solve the problem of navigating to a precise point in space; a rigid frame system to solve the problem of a consistent targeting; ionizing radiation to eliminate the problem of an invasive burr-hole and probe; multiple cross-firing radiation beams to create a method for concentrating energy on the target location, and the use of cobalt-60 practically generate a large number of small radiation beams.

Today, Gamma Knife® (Elekta, Stockholm, Sweden) radiosurgery (GKSRS) continues to be an outstanding example of the foundational principles of radiosurgery. The purposeful design of the Gamma Knife has survived decades of technological development in a form that would be easily recognized by Leksell, yet remains the reference standard against which competing technologies are judged. It has also heavily influenced the entire field of radiotherapy, inspiring the application of radiosurgical principles to indications outside of the head and continuing today in an escalating trend of dose hypofractionation and dose conformity.

History

Much has been written of the history of Gamma Knife radiosurgery. The interested reader is especially directed to a detailed recounting by Ganz [2]. In this section, we will summarize some important aspects of this history as it relates to creating integrated solutions to practical problems critical to the acceptance of radiosurgery as a discipline.

Early Vision and Initial System Designs

Leksell first attempted to realize the vision of his famous paper from 1951 [1] which introduced the concept of radiosurgery by treating two patients with trigeminal neuralgia, using the Gasserian ganglion as a target and a tightly collimated 280 kV X-ray beam as the energy source. While these cases were not published for many years [3], in 1954 Leksell reported the case of a patient treated for schizophrenia [4]. The report addressed his observations of the strengths and weaknesses of the technique, noting that higher-energy X-rays might have been advantageous and that perhaps particles such as protons should be considered.

After experimenting with proton beams at Uppsala starting in the 1960s [5] and finding them impractical, Leksell and his colleagues (Börje Larsson, Bert Sarby, and Kurt Lidén) investigated alternative radiation sources, settling on cobalt-60 due to its availability, relatively high photon energy (average 1.25 MeV), long half-life (5.26 years), and high specific activity, making it possible to use many small sources to make many small beams [6, 7]. They settled on a machine design that would use 179 stationary beams, elliptically collimated and arranged to have a precision of beam focus of 0.1 mm and a penumbra at the focus of 0.5 mm. This first gamma unit was constructed by the Mottola Company, and the first patients were treated in 1967 in Studsvik, the location of a Swedish nuclear research center and a convenient place to acquire and load cobalt-60 sources. Later that

D. P. Cordeiro
University of Virginia, Departments of Neurological Surgery, Charlottesville, VA, USA

D. J. Schlesinger (✉)
University of Virginia, Departments of Radiation Oncology and Neurological Surgery, Charlottesville, VA, USA
e-mail: Djs9c@virginia.edu

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year the device was moved to the Sophiahemmet Hospital in Stockholm. A second device was created for Leksell when he moved to Karolinska Hospital in 1975 [2].

From 1968 to 1983 Leksell and his colleagues treated 762 patients with Gamma Knife: 177 functional, 209 vascular, 342 tumor, and 32 diverse cases [8]. However, during this period, the entire worldwide reach of Gamma Knife radiosurgery was limited to Stockholm.

Revisiting the Design: The Gamma Knife Model U and Commercialization

The early experience of Leksell and colleagues demonstrated that Gamma Knife radiosurgery was useful for more than the originally planned functional indications [9–11], and word slowly began to spread. Lars Leksell, along with his sons Daniel and Laurent, founded Elekta Instrument, AB, in 1972 with the intention of commercializing Dr. Leksell's various neurosurgical innovations. The first Gamma Knife units outside of Sweden were in Buenos Aires in 1983 and Sheffield in 1985, both the result of personal inquiries by neurosurgeons who had visited Leksell in Stockholm. These units differed from the original prototypes by making use of 201 cobalt-60 sources and circular collimators which were better equipped to treat vascular malformations and solid tumors rather than only functional indications. As Elekta as of yet had no manufacturing capability, these two units were built by Nucletec SA, a subsidiary of Scanditronix Medical AB of Sweden [2, 12].

The first Elekta produced Gamma Knife was brought to the United States by Dr. Dade Lunsford at the University of Pittsburgh in 1987 [13]. This new model, termed the Model U, retained a design similar to the Buenos Aires and Sheffield units (as well as the original prototypes). This simplified regulatory approval in the United States as the original prototype had by this time been relocated to UCLA and was being used for research, so the model U was not considered a radical departure. The model U used 201 cobalt-60 sources of approximately 30 curies each. The patient was positioned in the unit in a supported supine, semi-upright position with the help of a hydraulic system, and a nearly hemispheric tertiary collimator "helmet" with either 4 mm, 8 mm, 14 mm, or 18 mm beams could be used to size each isocenter, or "shot." The unit was manually controlled; the neurosurgeon and the treatment team would manually set sliders on the patient's frame for the Y and Z coordinates and a trunnion system for the X coordinate. Individual beam channels could be replaced with solid "plugs" in order to block beams to protect critical structures. Elaborate protocols were required to ensure that no mistakes were made when setting coordinates and plug patterns, and treatments could often take hours to complete. As the unit opened like a clamshell in order to expose the sources, reloading the unit required removing it from the treatment vault and constructing a hot cell around it, using remote manipulating arms to remove and replace each source. Reloading was expensive and could require 4–6 weeks of downtime to complete (Fig. 1) [14].

Fig. 1 Gamma Knife® Model U (Elekta, Stockholm, Sweden) at the University of Virginia being prepared for source reloading. The clamshell design of the unit required it be removed from the treatment vault and placed in a temporary bunker

To address the problem of reloading and create a more commercially acceptable machine, in 1988, Elekta introduced a "model B" unit. The model B was a significant redesign of the system to permit a streamlined reloading procedure using an in-room "loading machine" which significantly simplified the time and expense of the process. The hydraulic system of the model U was replaced with a more robust electric system. The collimator retained the same beam sizes as the model U, but the patient was placed in a more supine position and the sources were arranged in five concentric rings in an annular hemispheric design. Because of regulatory complexities in the United States the model B was sold primarily in Europe and Asia [2, 12].

The manual nature of the model U and model B systems could make them cumbersome to use by a treatment team, prone to human error in setting the patient position, and quite slow in terms of total procedure time. Recognizing these problems required a solution, in 2000, Elekta introduced the "model C" unit. This unit introduced an "automatic positioning system," or APS, which could automatically position the patient's head at the correct stereotactic coordinate [15]. It also included GammaPlan® (Elekta, Stockholm, Sweden), an interfaced treatment planning system. The improved treatment planning capability made practical the use of multiple shots in a treatment and thus the ability to better conform to more irregularly shaped targets [16, 17]. A slightly upgraded "model 4C" followed a few years later.

By the mid-2000s, radiosurgery had gained significant traction as an efficacious treatment paradigm for a large

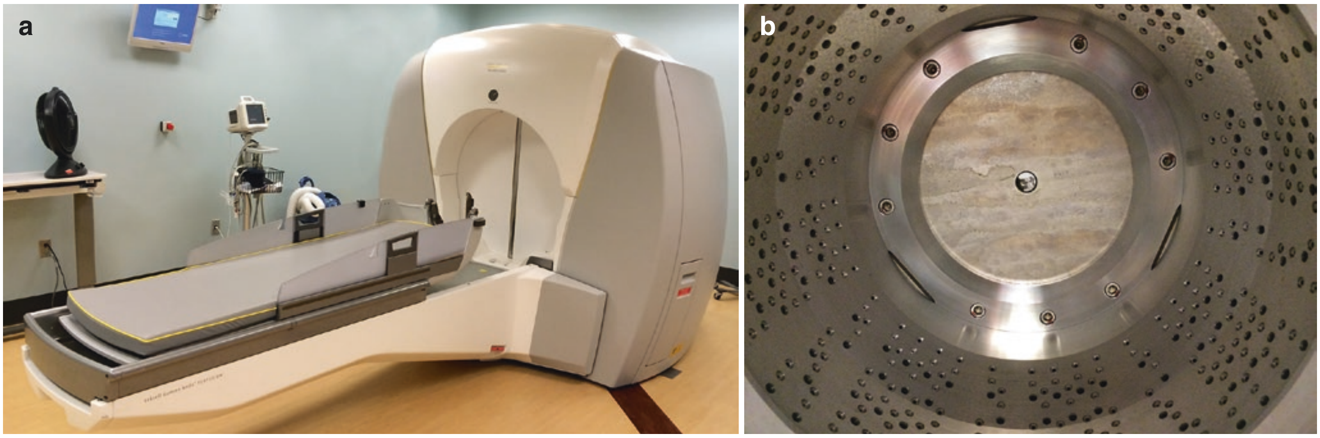


Fig. 2 (**a**, **b**) The Gamma Knife® model Perfexion™ (Elekta, Stockholm, Sweden) at the University of Virginia. (**a**). The Perfexion unit. (**b**) Closeup of the built-in collimator system of the Gamma Knife Perfexion. The beam channel pattern repeats eight times around the circumference of the collimator, matching up to eight source sectors

range of vascular, solid tumor, and functional indications, including for patients with more than a single tumor. Elekta completed work on a major paradigm change in 2006 with the release of the Gamma Knife Perfexion™ (Fig. 2a) with the aim of optimizing the unit for treating multiple lesions in a single setting and by greatly increasing the volume of a patient's head reachable by the system. The Perfexion also automates many treatment and quality assurance tasks, significantly increasing patient safety as well as decreasing beam-delivery uncertainties [18]. The resulting design included significant changes to the radiation unit, collimator, mechanics, patient positioning system, quality assurance tools, and treatment planning system.

The radiation unit of the Perfexion uses 192 cobalt-60 sources arranged in a cylindrical rather than the previous hemispherical geometry. The new geometry means the system has a variable source to focus distance. The previous external "helmet"-base tertiary collimator system is replaced with a single, integral tungsten collimator (Fig. 2b). Beam channels are machined into the collimator arranged in five concentric rings, with each ring containing 4 mm, 8 mm, and 16 mm beam channels as well as a blocked position. The beam channels are arranged in a way that the pattern repeats eight times over the circumference of the collimator, creating eight sectors. Matched to these sectors are the sources, which are no longer fixed in place, but instead are mounted on eight sliding carriages holding 24 sources each (one carriage per sector) that are driven by linear motors from the rear of the unit. The beam configuration of a given isocenter is set automatically by the system by moving each sector independently to any of the three beam sizes (or blocked) per the instructions in the treatment plan. Rather than manually plugging individual ports, an entire sector of sources may be blocked at one time. The system permits new isocenter configurations, as it is now possible to include mixed size isocenters (i.e., where different sectors have different beam sizes) [19].

Comparing to the older models, the treatable volume within the radiation cavity of the Perfexion is increased by 300%. The increase in the potential treatment volume enhances the ability of the system to treat patients with multiple lesions distributed throughout the brain in a single frame placement [20].

The automatic positioning system included with the model C is replaced by the Patient Position System (PPS) that instead of moving only the patient's head moves the whole bed to the desired treatment coordinates. The patient's head is fixed to PPS at one of three possible head angles (70°, 90°,110°) using an adapter which attaches to the stereotactic frame, and once attached the relative position of the patient's head and neck remains fixed throughout that part of the treatment, significantly increasing patient comfort. The PPS is controlled by a dual-encoder system that ensures the bed is at the correct stereotactic coordinates [18, 19].

Much of the quality assurance for the Perfexion has been similarly automated. Most significantly, a diode tool is included with the unit which through an automated routine determines the location of the radiation isocenter and compares this to a stored calibration value, with a difference that cannot exceed 0.4 mm. An installation diode tool ensures that all Gamma Knife Perfexion installations worldwide have absolute calibrations within 0.15 mm [21].

Evolution of Imaging and Treatment Planning for Gamma Knife Radiosurgery

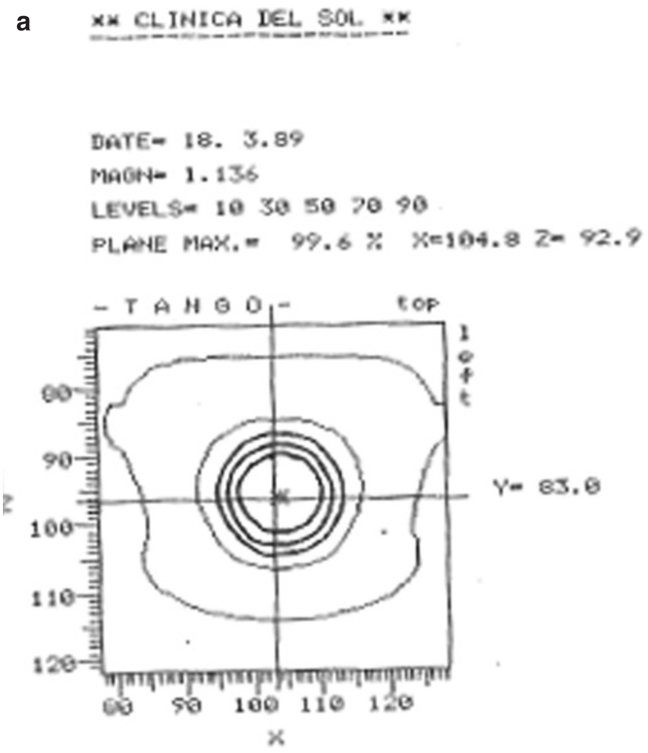
As imaging techniques evolved and computing power improved, so did the technology and techniques for radiosurgery treatment planning. At the time the Gamma Knife was first invented, planar X-rays were the state-of-the-art method for visualizing internal anatomy. In the brain, work on ventriculography and pneumoencephalography provided a rudimentary capability to resolve gross brain anatomy and in some cases solid tumors [22, 23]. In these early years of GKRS dose-planning programs did not exist. Treatment calculations were performed manually by the neurosurgeon and physicist. Precomputed isodose plots showing single-isocenter dose distributions in each plane could be overlaid on AP and lateral X-rays to identify the desired position of the isocenter. The required duration of the treatment was then calculated using a nomogram by the physicist via a combination of prescribed dose and location, using the average depth of the isocenter in the skull in the calculation [2]. The isodose distribution was assumed to be invariant to position, so absolute dose profiles could be understood by simply scaling according to the desired prescription dose. A bit later, depth calculations were refined to use distance measurements from ten preselected collimators in the collimator helmet to the skull surface. Treatment using multiple isocenters was extremely rare [24].

The introduction of tomographic imaging with the installation of a computed tomography (CT) system in Stockholm in 1973 changed the situation. In 1978 Elekta developed an attachment to fix the stereotactic frame to the CT scanner, permitting registration of the images to stereotactic space and usable for radiosurgery [25]. The three-dimensional imaging information led to a desire for a computerized treatment planning system that could make better use of the new imaging information. One such system was designed in the department of Radiophysics at the Karolinska, and another at A. B. Chinela Centro de Radiocirugia Neurologica in Buenos Aires [26] (Fig. 3a).

The first commercially available treatment planning system for the Gamma Knife was the KULA program (Elekta Instrument, AB) [24]. This program used as an input the shape and size of the skull, calculated from a plastic measuring helmet (termed the "bubble" helmet) which permitted radial measurements taken along predefined measurement vectors rather than through beam channels in the collimator helmet. The system was limited in that manipulating images in real time was not yet possible; treatment planning remained a lengthy procedure. The results of the plan were plotted graphically using a pen and ink plotter on transparency sheet, which could be overlaid on printed films to verify isocenter and isodose distribution locations (Fig. 3b).

Meanwhile, in the 1980s the first MRI units were being introduced into the clinic [27, 28]. MR imaging provided vastly improved soft tissue resolution, greatly reducing the visualization uncertainty of targeted disease and surrounding normal tissue structures. As MR pulse sequence design progressed and MR installations became widely adopted, MR became the imaging standard for Gamma Knife cases. Over time, a variety of pulse sequences were incorporated that could be used to highlight different aspects of brain anatomy including sequences to highlight detailed anatomical structures within the cerebrospinal fluid space [29], parasellar region [30], and sequences useful for visualizing subcortical gray matter structures [31]. More recently, perfusion [32] and diffusion [33, 34] sequences have been adopted which can provide physiological as well as anatomical information to help inform a treatment plan.

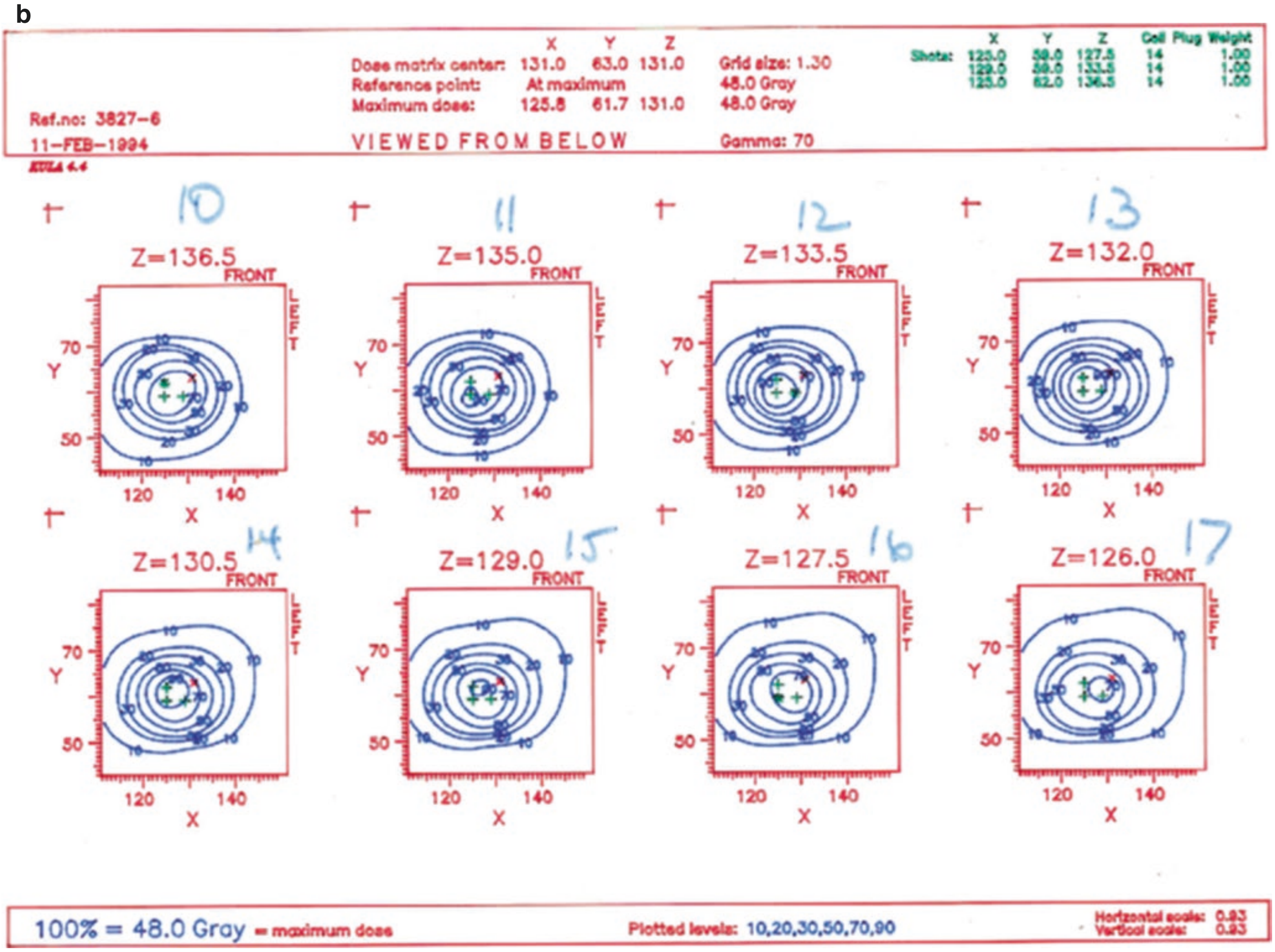
In part to harness the rapid improvements in imaging technology, in 1991 a major upgrade to the treatment planning system was released in the form of GammaPlan® (Elekta Instrument, AB). GammaPlan introduced several major advancements, including the ability to load and manipulate DICOM-based images of a variety of modalities including CT, MR, and angiography; networking to allow these images to be sent directly to the workstation from the imaging suites; contouring and measurement tools such as dose-volume histograms to make it possible to more carefully evaluate dose-volume coverage and constraints to targets and organs at risk; and a direct serial interface to the treatment unit to allow plans to be transferred without risk of human error. Multiple isocenter plans were directly supported, and


** CLINICA DEL SOL **

DATE= 18. 3.89
MAGN= 1.136
LEVELS= 10 30 50 70 90
PLANE MAX.= 99.6 % X=104.8 Z= 92.9

Fig. 3 (a–c) The evolution of Gamma Knife® (Elekta, Stockholm, Sweden) treatment planning. (a) The Tango treatment planning system used at the Centro de Radiocirugia Neurologica in Buenos Aires. (b). The output of the KULA treatment planning system drawn on a transparency by a computer plotter. (c). A screenshot of the dose comparison workflow in Leksell GammaPlan®

b



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KULA 4.4

	X	Y	Z	
Dose matrix center:	131.0	63.0	131.0	Grid size: 1.30
Reference point:	At maximum			48.0 Gray
Maximum dose:	125.8	61.7	131.0	48.0 Gray

VIEWED FROM BELOW

Gamma: 70

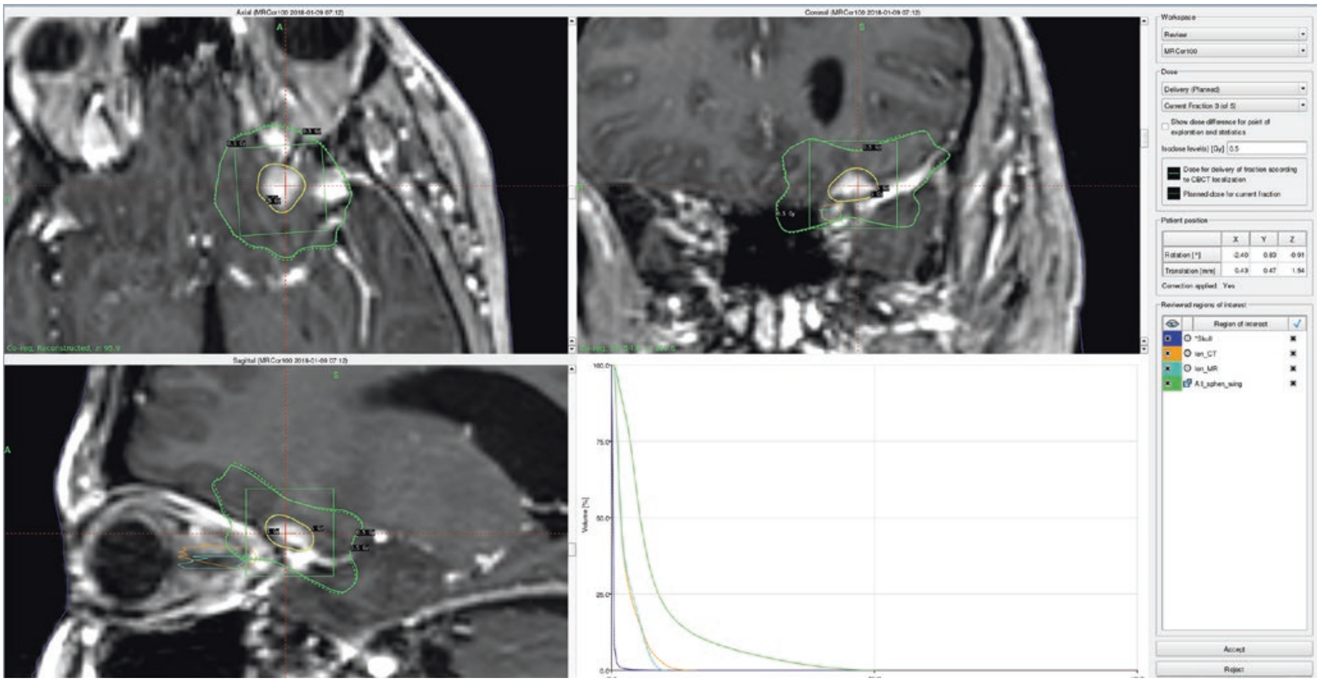
	X	Y	Z	Coll	Plug	Weight
Shots:	125.0	59.0	127.5	14		1.00
	129.0	59.0	133.5	14		1.00
	125.0	62.0	136.5	14		1.00

100% = 48.0 Gray = maximum dose

Plotted levels: 10,20,30,50,70,90

Horizontal scale: 0.93
Vertical scale: 0.93

c



Workspace
Review
MRCor100

Dose
Delivery (Planned)
Current Fraction 3 (of 5)
☐ Show dose difference for point of exploration and statistics
Isodose level(s) [Gy] 0.5
Dose for delivery of fraction according to CBCT localization
Planned dose for current fraction

Patient position

	X	Y	Z
Rotation [°]	-2.40	0.83	-0.91
Translation [mm]	0.43	0.47	1.54

Correction applied Yes

Reviewed regions of interest

Region of interest	✓
*Skull	✖
lon_CT	✖
lon_MR	✖
A.I_sphen_wing	✖

Fig. 3 (continued)

differential doses could be prescribed to different targets by "scaling" the dose to different dose calculation "matrices." GammaPlan continues to evolve today; the current version (Fig. 3c) and runs on personal computer hardware platforms with high-end graphics processors and networking solutions that allow the treatment planning system to communicate with multiple imaging providers and multiple Gamma Knife treatment units.

Recent Developments: Hypofractionation and Onboard Image Guidance

Certain clinical situations are not amenable to single-fraction radiosurgery, including large tumors or tumors situated very close to radiosensitive normal anatomy [35, 36]. There are also patients who are not ideal choices for a stereotactic frame placement. Recent developments in GKSRS were motivated by a desire to provide options for multi-session radiosurgery using alternative immobilization techniques to replace the traditional stereotactic frame. These developments include the Extend System, built on top of the Gamma Knife Perfexion platform, and the recently introduced Gamma Knife Icon system.

Extend™ System for Gamma Knife Perfexion

The Gamma Knife Extend System (Elekta, Stockholm, Sweden) represents a first attempt at replacing the absolute need for a fixed stereotactic frame system with a less-invasive, relocatable frame system that would be practical in a multi-fraction/multi-session setting. The Extend System consists of several components; a patient-specific immobilization device comprised of a carbon-fiber, dental-impression assisted frame and vacuum cushion; a monitored vacuum system interlocked to the Gamma Knife control system; and a measurement template and associated digital measurement probes. Each patient is fitted for a dental impression of the upper palate which is attached to the front plate of the frame system. A rigid head-pillow is created by removing air from the vacuum cushion. The front plate of the frame system is then attached to the body of the frame system and the position of the dental impression remains locked for the duration of the treatment course. The front plate can be attached and removed from the back of the frame system to permit multiple treatment fractions and imaging sessions. Planning CT images of the patient are acquired with the frame and an associated imaging box after taking a reference set of measurements with the digital measurement probes. These images are co-registered to other volumetric (CT/MR/PET) imaging and used for treatment planning. Prior to a treatment session, the patient is set back up on the treatment bed with the frame attached. The treatment team works with the patient to adjust position until the digital measurement probes agree to within a small tolerance (on the order of 1 mm) of the planned position. During treatment, the vacuum system monitors the vacuum level to the mouthpiece of the system as a proxy for motion. If the vacuum level drops, the treatment pauses automatically and new measurements/adjustments of position are completed [37]. Treatment uncertainties and the use of the vacuum surveillance system as a proxy for patient motion were both found to be satisfactory for use in a multi-session radiosurgery setting [38, 39].

Gamma Knife Icon™

The Extend System for the Gamma Knife succeeded in its goal of providing a practical, albeit sometimes cumbersome, option for multiple fraction treatments. The latest release of the Gamma Knife, the Icon model (Elekta, Stockholm, Sweden), rethinks the solution entirely and introduces onboard image guidance and intrafraction motion management capabilities to allow patients to be treated without a frame at all, instead of using thermoplastic mask immobilization for multisession treatments [40].

The overall Gamma Knife Icon design is similar to the Perfexion model. The primary modification is the addition of a cone-beam computed tomography (CBCT) system and an infrared motion tracking system known as the intrafraction motion management (IFMM) system (Fig. 4). The CBCT system is designed in a novel, double-hinged form-factor. The imaging gantry lowers into scanning position at the same time as the PPS moves the patient to the end-scanning position. The imaging gantry then rotates again to reach the starting scan position. During imaging, the scanning arm rotates 200 degrees in approximately 30 seconds, with a 1000 mm source to detector distance. The scanner uses 90 kVp X-rays and two preset imaging modes. In both cases, the resulting images are reconstructed from 332 projections, and a voxel size of 0.5 mm, and an image volume of 448 mm^3 voxels [41, 42]. The imaging isocenter of the CBCT system has a known calibrated relationship to the radiation isocenter of the system, meaning that the resulting CBCT images can be used as the basis for stereotactic targeting [43]. The IFMM system is a stereoscopic infrared camera system that tracks the position of a small reflective sticker that can be placed on a patient's nose relative to reference markers placed on posts attached to the back-plate of the immobilization system [44].

The Icon system provides several new potential treatment workflows [45]. Patients may be treated in a thermoplastic mask using a CBCT as reference stereotactic coordinates. Prior to each treatment, the patient is set up on the machine in the thermoplastic mask, a new CBCT is acquired, and the treatment plan is shifted to match the current stereotactic

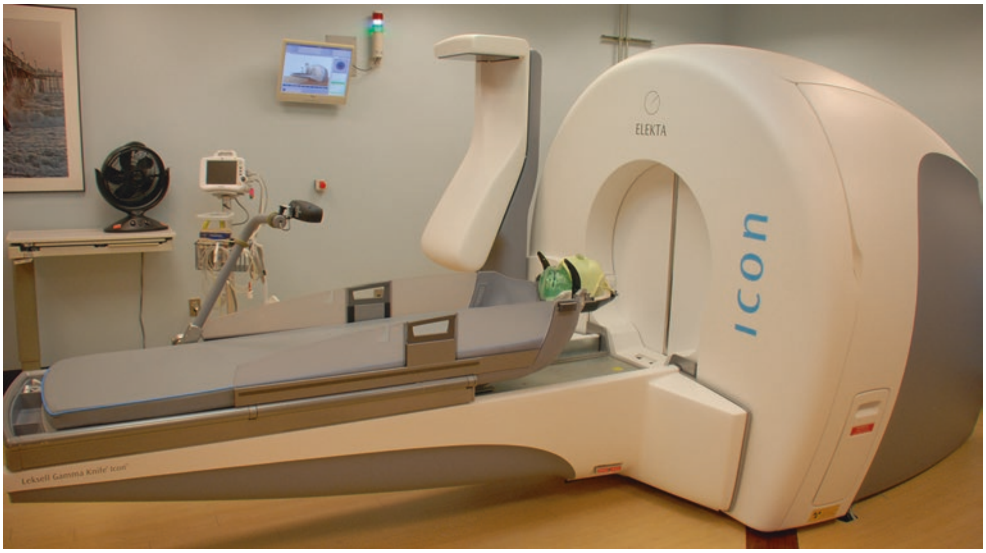


Fig. 4 The Gamma Knife model Icon™ (Elekta, Stockholm, Sweden) at the University of Virginia. This unit was upgraded in-place from the Perfexion™ model of Fig. 2. Notice the cone-beam CT scanning gantry and the intrafraction motion management camera that make possible GKSRS treatments with a thermoplastic mask

position of the patient. During treatment, the IFMM tracks the patient's nose marker. If it drifts out of position beyond some tolerance, the beams will gate to a blocked position. Beams will resume if the patient returns to the planned position within a short time interval; if not the patient will pause, a new CBCT can be acquired. The ICON system may also be used with a traditional stereotactic frame. In this workflow, the CBCT can be used as a valuable last-minute quality assurance check of the patient's frame and stereotactic position.

Limitations of Gamma Knife Stereotactic Radiosurgery

The design of the Gamma Knife is well-matched to the task of intracranial radiosurgery. The use of radioactive sources as a source of radiation and a radiation body and collimator system with an essentially fixed geometry specifically designed to receive a patient's head make it an elegant, extremely reliable intracranial radiosurgery solution. However, these design choices also drive the primary limitations of the technique.

Restriction to Intracranial Indications

Perhaps the most prominent limitation of Gamma Knife radiosurgery is that it is restricted to treating the head and at most the upper cervical spine indications. Targets inferior to the C2 vertebrae are difficult or impossible to treat, partly limited by the available space to correctly position the target at isocenter without colliding with the top of the cranium, but more importantly because it is practically difficult to immobilize the spine inferior than the C2 level [46].

Long Beam-Delivery Duration

A newly loaded Gamma Knife has a dose rate (as measured at the center of a 8 cm diameter spherical plastic phantom using a 16 mm collimator) of between 3.0 and 4.0 Gy/min (compared to ~14Gy - 24Gy/min for a linear accelerator equipped with a flattening-filter-free (FFF) treatment mode.). This base dose rate is further reduced by radioactive decay and during a given treatment the output factors for the different collimator sizes used. Beam-on time for the Gamma Knife can thus be long and the beam time scales linearly with the number of lesions treated [47]. This would seem to compare negatively against recent developments in linac radiosurgery, especially single-isocenter VMAT techniques which have an approximately constant beam time regardless of the number of lesions treated [48]. However, if one compares the total procedure time, including simulation, treatment planning, and patient-specific quality assurance then the total procedure time of the Gamma Knife compares favorably [49]. Dosimetric studies also show a tradeoff between the speed of VMAT treatment delivery and the magnitude of low dose spill to normal brain [47, 50, 51], as well as the potential for targeting errors due to rotational setup uncertainties [52]. However, both techniques achieve similar dosimetric metrics such as tumor coverage and conformity index and image guidance can potentially minimize any setup uncertainty [53].

Dose Rate Decay and Potential Implications for Radiobiological Effectiveness

The radioactive decay and commensurate decrease in the dose rate could potentially reduce the biological effectiveness of the procedure as the lower dose rate affords cells' time for repair of sublethal DNA damage. Several studies have examined this hypothesis with mixed results. Niranjan and colleagues examined 9 L rat gliosarcoma cells and found no statistical difference in cell survival over a range of dose rates representing greater than two half-lives of 60Co [54]. Balamucki and colleagues retrospectively analyzed data for 239 patients treated for trigeminal neuralgia and when controlling for other variables found no correlation between the dose rate and pain control [55]. In contrast, Lee and coauthors investigated 133 trigeminal neuralgia patients who were treated over the duration of slightly more than one half-life of source decay. Patients were administered a standardized pain scoring test before GKRS and at first follow-up (mean 1.3 months). Serial follow-up phone calls were used to obtain information on pain recurrence. Both short and long term results correlated with dose rate; with patients treated with higher dose rates experience greater decreases in pain and fewer recurrences [56].

Requirement for Source Reloading

The use of radioactive material-based sources allows the Gamma Knife to create extremely stable beams of radiation quite reliably. As there are few electronic or moving parts, Gamma Knife units tend to have extremely infrequent downtime [57]. However, the radioactive sources are also a limitation. The sources require replacing to prevent the dose rate of the machine from become so low that radiobiology is affected or that patients will not accept the duration of the procedure. Source reloading remains an extensive procedure that requires several weeks of downtime and a significant amount of coordination.

Future Directions

The history of Gamma Knife radiosurgery has always involved the integration of new technologies as they have reached the clinic. After many decades of development, treatment delivery with the Gamma Knife has matured. The next phase of the evolution of Gamma Knife radiosurgery (and radiosurgery in general) will likely focus on methods for stimulating the body's own immune system to help fight disease, complementary therapies that may help trigger these immune system effects, and harnessing the vast amounts of imaging and dosimetric data created during the radiosurgery process which can better inform patient selection, evaluation of treatment efficacy, and clinical decision-making.

Perhaps the most significant near-term future development may be the recruitment of the body's own immune system to help control and even cure malignant disease. Radiosurgery is by definition a local treatment. Although progression-free survival is an often-reported endpoint for clinical radiosurgery outcome studies, in reality the degree and duration of local tumor control has always been the most logical outcome for SRS. Patients with metastatic disease are often managed with systemic treatments such as chemotherapy or whole-brain radiotherapy for overall disease control. However, hints published in the literature of the so-called abscopal effect [58], combined with a much more nuanced understanding of the local tumor immune environment [59] have inspired efforts to try to use focal treatment such as radiosurgery to create cellular "debris" which can be detected by the immune system and used as the basis for a systemic response [60].

Help in this regard may come from alternative treatment modalities that can complement the strengths and weaknesses of radiosurgery. Several emerging technologies use heating as opposed to high-dose ionizing radiation to achieve ablative levels of cell death within small volume targets. Two examples are high-intensity focused ultrasound (HIFU) [61, 62] and laser interstitial thermal therapy (LITT) [63]. HIFU and LITT can be combined with near-real time MR-thermometry [64] for image guidance. Energy deposited as heat from lasers or ultrasound has several attractive characteristics; it is nonionizing; it can be repeated; the biological effect is much faster than for ionizing radiation; it is effective under conditions of hypoxia where ionizing radiation can be less effective; and the effect is deterministic. The technologies can be used to deliver therapeutic payloads in microbubbles, selectively open the blood-brain barrier, and potentially create heat-shock proteins and other cellular debris which be used to prime the immune system [65, 66].

The widespread deployment of parallel computing technologies such as graphics processing units (GPUs) and especially cloud computing infrastructures has created significant opportunities to apply large increases in computing power to the clinic [67, 68], including radiosurgery. Dose calculations and image processing pipelines are well-suited to parallelizable hardware architectures such as those offered by onboard GPU chips. These can create order-of-magnitude increases in dose calculation speed, helping to make techniques such as inverse treatment planning fast enough to be clinically practical in a single-fraction environment where patients are waiting for treatment with headframe fixation. GPU-enabled algorithms have made tremendous impacts in a variety of radiotherapy scenarios, and could have an equally important impact on Gamma Knife radiosurgery.

Cloud computing infrastructures make possible the storage and computation of large datasets that would be impractical to analyze on one or a few computers. This in turn has led to the rise of a series of techniques termed “Radiomics,” where large numbers of image features are extracted from large numbers of image sets and then analyzed for patterns that correlate with various clinical features [69–71]. Radiosurgery commonly involves imaging from several MR pulse sequences and frequently also includes CT, PET, and X-ray imagery at the time of treatment planning. Patients often have pretreatment and serial posttreatment imaging as well. Radiomics analysis of these data may help to enhance our ability to evaluate treatment efficacy and make informed clinical conclusions about local failure vs. adverse treatment effect.

The potential for Radiomics to make a difference will itself be enhanced by steady improvements in imaging. Newer MR pulse sequence techniques such as diffusion imaging, perfusion imaging, and MR spectrography will help bring functional information into the treatment planning process as well as to posttreatment evaluation. Advances in PET imaging, and in new combined modalities such as PET-MR [72] will complement these new MR pulse sequences. Emerging imaging modalities may also play a role, perhaps 1 day including photoacoustic tomography [73, 74], which can image to extremely high-resolution in near real time, and can use a variety of molecules as intrinsic contrast agents to make possible the visualization of entire vascular trees, oxygen transfer, and even individual circulating tumor cells.

However, perhaps the most important development of the next 10 years may be the continuing rapid advance of machine learning. Machine learning technologies such as deep convolutional neural networks [75] have been revolutionizing a wide range of industries, and radiotherapy is no exception [76]. Machine learning techniques may 1 day make it possible to fully automate the treatment planning process and may create important new opportunities to evaluate treatment efficacy and predict the future course of disease on a per-patient basis. This in turn may help make radiosurgery a much more personalized treatment experience.

Practical Considerations

The workflow and indications for GKSRS have been refined and matured over many years of experience and many generations of technological advancement. However, SRS remains a treatment technique requiring extreme care and attention to detail. The authors believe the practical considerations summarize in Table 1 can help when beginning a new GKSRS program.

Table 1 Practical considerations when considering a GKSRS program

Key consideration	Description/rationale
Credentialing and training	GKSRS is a specialized procedure requiring specialized training. The planning process and patient workflow differ significantly from other radiation therapy techniques. Formal institutional criteria for credentialing and training can help to prevent mistake [77]
Care during commissioning and QA	The precision and accuracy required for GKSRS is demanding. Careful commissioning and quality assurance maximize the probability of detecting any problems before they reach the patient during treatment
Patient selection	Understanding of the indications and contraindications for GKSRS is a critical part of practice
Proper understanding of dose/dose limitations	Prescription dose and dose/fractionation schemes should be well supported by published evidence. Deviations should occur only under in the settings of multi-institutional or single-instruction trials under the supervision of an institutional review board
Balance between time of treatment and the “perfect” plan	Conformity of the prescription isodose to the target is one measure of a plan’s fitness. However, the best plan is often a balance between many factors, including dose falloff, beam-on time, and dose to nearby normal anatomy
Icon – new flexibility in workflow requires careful attention to process	The Gamma Knife Icon provides several new possible treatment workflows. This flexibility requires extra vigilance to prevent mistakes
Consider total workflow when thinking of time differences between Gamma Knife and other modalities	One potential shortcoming of GKSRS is the longer beam-on time as compared to a high-dose rate linear accelerator. However, the required treatment time should be considered as one part of a longer treatment process. If one factors in the relative simplicity and speed of treatment planning and quality assurance, as well as overall plan quality, the beam-on time differences may not be as significant

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