



## History of Gamma Knife Surgery

### Milestones

- 1951 Leksell, professor in Neurosurgery in Sweden, introduces the concept radiosurgery
- 1967 the first Gamma Knife prototype is made and the first patient treated at Studsvik nuclear plant
- 1968 the first patient treated at the Karolinska, Sophiahemmet Hospital in Stockholm, Sweden
- 1969 the first acoustic neuroma patient treated
- 1969 the first patient with a pituitary adenoma treated
- 1970 the first patient with an arteriovenous malformation treated
- 1974 an improved Gamma Knife prototype installed at the Karolinska Hospital in Stockholm
- 1974 introduction of the first computer assisted dose planning program for the Gamma Knife
- 1976 the first patient treated for meningioma
- 1985 new Gamma Knife prototypes delivered to Sheffield, U.K., and Buenos Aires, Argentina
- 1987 the first Gamma Knife model for serial production installed in Pittsburgh, USA
- 1988 Gamma Knife series B installed at the Karolinska Hospital, Sweden
- 1989 the first publication on gamma knife surgery for cerebral metastases
- 1990 introduction of the Leksell Gamma Plan dose planning program
- 1995 International Stereotactic Radiosurgery Society (ISRS) Fabrikant Award to Drs Larsson and Backlund for work with the Gamma Knife
- 1996 Image fusion between CT and MRI available in the Leksell Gamma Plan
- 1997 ISRS Fabrikant Award to Dr Lunsford
- 1998 Semiautomatic outlining of target volumes available in the Leksell Gamma Plan
- 1999 ISRS Fabrikant Award to Dr Lindquist of the Cromwell Hospital
- 2000 Introduction of the Model C, using the automatic Positioning System (APS), allowing remote movement of the patient during treatment.
- 2003 Cromwell Hospital gained NHS Accreditation
- 2006 Cromwell treated 1000 patients
- 2006 Introduction of the Gamma Knife Perfexion
- 2007 Gamma Knife Perfexion installed at the Cromwell Hospital 2nd in the world.

### The Gamma Knife

After the Second World War Lars Leksell (1907-1986), Professor of Neurosurgery in Lund, Sweden and later at the Karolinska Institute in Stockholm started to work on a stereotactic instrument for image guided intervention into the deep parts of the brain. In the Leksell stereotactic system, an arc carries the tool, which is introduced into the brain guided by an image obtained with the stereotactic instrument in place. The target point should coincide with the center of the arc. The arc can even be rotated around its axis, and the target is still reached when the instrument is advanced to the

center of the arc. It soon occurred to Leksell that an x-ray tube could be “the surgical tool” placed on the arc. The X-ray tube could fire beams from various positions of the arc to a focal point in its center. Each individual x-ray trajectory would deliver a harmless dose of radiation but where the beams crossfired, destructive damage could be achieved. The idea was to destroy the target volume in a single session avoiding harmful radiation to the surrounding normal tissue. Employed in this way, photons will work as other physical agents used inter-operatively in neurosurgery such as laser beams or ultrasound. For this new way of employing x-rays, Leksell coined the term radiosurgery. The energy delivered from a conventional X-ray tube proved to be insufficient for the purpose and other sources of radiation were considered. Thus linear accelerators were considered but found to be deficient in precision and accuracy. Leksell and Larson then explored the possibility of using protons produced by a synchrocyclotron. The equipment needed for delivering protons is, however, extremely costly and the technique is still used in only a few centers throughout the world. It was realized that the search for more user-friendly equipment for delivering ionizing radiation had to go on. The alternative to using an accelerator indirectly producing photon energy in the form of x-rays would be to use photons or gamma rays produced by the natural decay of radioactive isotopes. The choice was <sup>60</sup>Cobalt. Larson and Leksell designed the first multi-cobalt unit in the late 1960’s. The first “multi-cobalt unit of Leksell” was constructed and delivered from the oldest manufacturing plant in Sweden, Motala Verkstad, in 1967. At the nuclear plant in Studsvik, south of Stockholm, the device was loaded with 179 sources of <sup>60</sup>Cobalt. The arc principle of the Leksell stereotactic system was utilized. The patient’s head had to be positioned within a secondary collimator helmet on the treatment couch so that the intended target point coincided with the focus of the beams in the center of the collimator helmet. The first patient was treated at the loading site in Studsvik in November of 1967. The unit was then installed at the “Sophiahemmet” hospital in Stockholm. In February 1968, a cancer patient suffering from intractable pain was the first patient to be treated there. A small lesion was made in the medial thalamus and the outcome was a success. The dose required to make a lesion in the normal brain was based on data from animal experiments. The available imaging modalities did not allow corroboration of the lesion. However, the first patients treated were terminally ill cancer patients with intractable pain, and the lesions could be studied at autopsy. It was concluded that a target dose of 180 Gy was required to make lesions, which were around 200 cc in volume. These single doses were 3-5 times the total doses used in conventional radiotherapy.

The first prototype Gamma Knife was specifically designed to create the small brain lesions used in functional neurosurgery. The original prototype was also used for the first treatment of acoustic neuromas, craniopharyngiomas, and arteriovenous malformations. Because of the small radiation fields, only small pathological volumes could be treated. Thus the first acoustic neuroma treated by Lars Leksell in 1969 was small but tumor control was achieved until the patient’s death from intercurrent disease in 1998. The first patient with an arteriovenous malformation treated by Ladislau Steiner, and Lars Leksell in 1970 was a patient with a relatively large occipital malformation, and the radiation was directed at two afferent arteries only. The result was dramatic and after 2 years, the malformation could no longer be visualized by arteriography. This initial success contributed to a rapid development of radiosurgery. The commencement of treatment of tumors and vascular malformations emphasized the need for larger radiation volumes.

The second prototype of the Gamma Knife was installed at the Karolinska hospital in 1974. The unit had been modified to accommodate other than functional disorders.

The diameter of the secondary collimator helmets were larger. The pioneering results 3 by Leksell's team were published on AVM by Ladislau Steiner and Christer Lindquist, on craniopharyngiomas by Eric-Olof Backlund, on acoustic neuromas by George Nore'n, and on Cushing's disease by Tiit Rähn. Because there was no previous experience on clinical use of single session high, dose radiation to rely upon progress was slow. Before a new patient was treated, the previous case was followed for a relatively long time. Therefore, from 1968 to 1988 only a moderate number of patients were treated.

A number of international visitors flocked to the neurosurgery department of the Karolinska Institute to learn Leksell's stereotactic technique. Prominent neurosurgeons tried to obtain their own Leksell multi-cobalt units but local regulations, skepticism and financing were obstacles to many of them. The renowned microneurosurgeon, Dr Robert Rand, in Los Angeles bought the first prototype of the gamma Knife for a nominal fee of \$1.00 from the Karolinska Institute. It was used for animal experiments at UCLA, Mr. David Forster in Sheffield, UK, and Drs Roberto Chescotta and Hernan Bunge in Buenos Aires were the first to order custom-made units for their neurosurgical programs. This happened in 1985. The Sheffield Unit was installed under the auspices of the National Health Service of the United Kingdom, and the Buenos Aires Unit was installed in a private hospital. A significant improvement in these custom-made units was a further enlargement of the collimator helmets. This allowed easier access to peripheral parts of the brain. More significantly, it allowed introduction of the stereotactic frame. Thus, the frame could be used for imaging the target and as a head holder in the treatment unit. In the first unit, the frame could only be used as a localization device because of mechanical constraints in the collimator helmet.

In the second prototype Gamma Knife, there were still mechanical constraints and treatment of lateral targets was difficult. The increased use of the Gamma Knife for treatment of tumors also demanded the possibility of more convenient irradiation for larger target volumes. These factors were borne in mind when the first commercially launched Gamma Knife was designed. The first delivery was made to the University of Pittsburgh of this model in 1987. The collimator helmets were more spacious and a 4th helmet with a beam width of 18 mm at the focal point was added. The Pittsburgh unit was the result of a long battle for recognition of radiosurgery. Fellow neurosurgeons had to be convinced of efficacy and regulatory committees of safety. Dr Dade Lunsford shepherded it successfully through a maze of bureaucracy. In 1980 Dr Lunsford had been a van Wagenen fellow in the neurosurgery department at the Karolinska. During this time he worked closely with Professor Leksell and acquired skills in stereotactic neurosurgery. Dr Ladislau Steiner, the foremost representative of Leksell's School of Radiosurgery, retired from the Karolinska in 1986. He was therefore available to introduce gamma knife surgery to launch their radiosurgical program. He then moved on to become Professor of Neurosurgery and Director of the Lars Leksell Gamma Knife Center at the University of Virginia in Charlottesville where he is still practicing. Gamma Knife technology then rapidly spread across the United States with new installations in Dallas, Chicago, the Mayo clinic, University of California and other renowned neuroscience centers. The first commercially available Gamma Knife, the model U, required the construction of a "hot cell" for isotopeloading purposes. The next generation of Gamma Knives, the models B, introduced at the Karolinska Hospital in 1988 therefore had a different configuration of the radiation sources in order to facilitate its loading. The 201 sources were arranged in 4 a toroidal fashion. This ring-like structure can be rotated like a magazine of a revolver and access gained to radioactive sources through a

small slot in the outer shielding. A purpose built loading device can therefore be used for loading and reloading. Further improvements of the B unit resulted in model C. This model is similar in most respects to the B model but has the addition of an automatic positioning system. For multi-isocenter treatments, the patient does not need to be manually removed from the couch helmet. Micromotors connecting the couch mounted collimator helmet and the stereotactic frame are used for co-ordinate adjustments.

## Evolution of Dose Planning

Dose planning was developed in parallel with improvements of visualization techniques. For treatment in the first prototype Gamma Knife, dose distribution was approximated to be the same for every patient. The radiation time was calculated based on the half-life of Cobalt and the distance from the sources to the target based on ruler measurements from the collimator helmet to the surface of the patient's head. In 1974, dose planning was aided by the introduction of computer calculations. The computer calculated the dose absorbed in points within a box 31 x 31 x 31 in size. The calculations were based on the approximate position of the target volume in the head measured with a ruler from a x-ray of the head. Lines connecting points calculated to receive a similar dose, isodose lines, were printed on transparent paper. The isodose lines through any stereotactic plane of choice could be printed with a magnification similar to that of the stereotactic image. The dose distribution was displayed by overlaying the transparencies onto the stereotactic image. Before computers became available, most treatments were made with only one target point or isocenter. The addition of even only one additional isocenter made calculations of the resulting isodose configuration uncertain. The computerized dose-planning program "KULA" opened the possibility to prescribe multi-isocenters and thus significantly increased conformity between prescribed dose and target volume. However, the available computers were very slow and each calculation could take 10- 20 minutes. For practical purposes, time could not be spent on too many changes of the dose plan. The quality of the dose plan therefore relied very much on the dose planning experience of the neurosurgeon and his physicist. The rapid development of computer technology facilitated the introduction of user-friendlier dose planning programs. In 1990, the "Gamma Plan" was introduced. In the system, the digital image information could be transferred to the dose-planning computer and dose-plans could be made directly on the images in seconds. It now became practical to use not only two but multiple isocenters to get excellent conformity between the prescribed radiation volume and the target volume. The software for the first time also included facilities for quality assessment of the treatment. Dose volume histograms portray the quality of treatment within seconds. This dose-planning system has undergone several further improvements. One of the more significant was the introduction of image fusion in 1996. This software makes it possible to blend CT and MR images for optimal visualization of the target area. In 1998, software development made it possible to detect gray scale differences in MR and CT images. Semi-automatic timesaving outlining of target volumes can be made with this facility with a so-called segmentation technique.