GAMMA CAMERA. See ANGER CAMERA.

GAMMA KNIFE

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INTRODUCTION

The Leksell Gamma Knife is one of the most massive and costliest medical products ever created (see Fig. 1). It is also one of the most clinically and commercially successful medical products in history, with > 180 units installed worldwide at this writing. The device is used exclusively for the treatment of brain tumors and other brain abnormalities. The Gamma Knife, also known as the Leksell Gamma Unit, contains 201 sources of radioactive cobalt-60, each of which emits an intense beam of highly penetrating gamma radiation (see Cobalt-60 units for radiotherapy). Due to the penetrating nature of the gamma rays emitted by these radiation sources, the device must be heavily shielded, and therefore it weighs ~ 22 tons. The Gamma Knife must also be placed in a vault with concrete shielding walls 2–4-ft thick.

This remarkable device is used in the following way: A patient known from prior medical diagnosis to have a brain tumor or other treatable brain lesion, is brought to a Gamma Knife Center on the selected day of treatment. Gamma Knife treatment is thus intended for elective surgery and is never used for emergency purposes. The patient is prepared for treatment, which normally occurs with the patient alert and awake, by a nurse. Then, a neurosurgeon injects local anesthetic under the skin of the forehead and posterior of the skull. He/she then affixes a stereotactic head frame (see Fig. 2) with sharp pins to the patient's head (much like a halo fixation device for patients with a broken neck). The patient is transported by wheelchair or gurney to a nearby imaging center where a Computed Tomography (CT) X-ray scan or a Magnetic Resonance Imaging (MRI) scan of the brain (with the stereotactic head frame on) is obtained (see articles on Computed Tomography and Magnetic Resonance Imaging). Specially constructed boxes consisting of panels containing geometric localization markers are attached to the stereotactic frame and surround the patient's head during imaging. The markers contained in the localization boxes are visible on the brain scan, just outside the skull (see Fig. 3). All imaging studies are then exported via a PACS computer network or DAT tape (see the article on Picture Archiving and Communication Systems) into a powerful computer, where a treatment plan is created. A neurosurgeon, a radiation oncologist, and a medical physicist participate in the planning process. When the plan is satisfactorily completed, the patient (still wearing the stereotactic frame) is brought into the treatment room. The patient is then placed on the couch of the treatment unit and the stereotactic frame is docked with the trunnions affixed to the helmet (see Fig. 4). After the staff members leave the room and the room shielding doors are closed, the Gamma Knife vault door automatically opens and the patient couch is pushed forward into the body of the device, so that the holes in the collimating helmet line up with the radiation source pattern inside the central body of the device. The treatment begins at that point. Any given patient may be treated in this manner with a single "shot" (e.g., treatment) or with

Figure 1. The Leksell Gamma Unit Model U for treatment of patients with brain tumors and other brain abnormalities.

Figure 2. Patient with Leksell Model G stererotactic frame affixed to their head. This frame restricts patient motion during imaging and treatment and also allows placement of fiducial markers to localize the volume to be treated.

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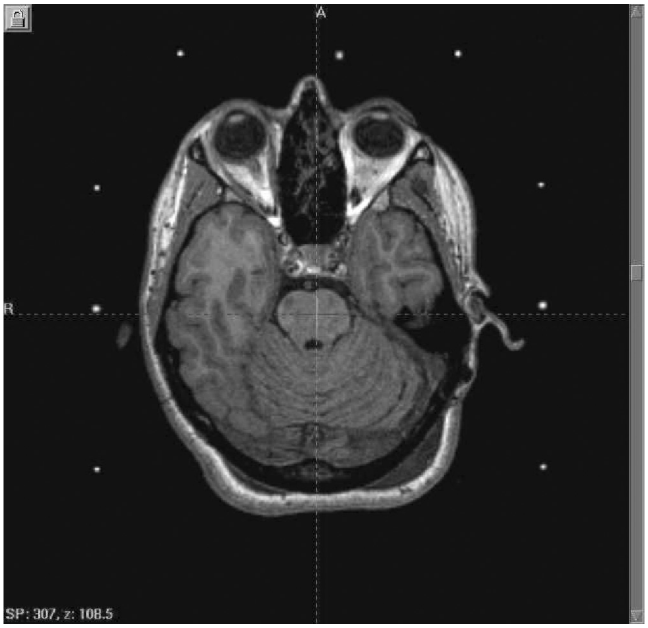

Figure 3. Axial MRI scan of patients brain, with external fiducial markers filled with copper sulfate solution to enable localization of target volumes.

many shots (30 or more in some cases). The collimating helmet may be changed to use one or more of the available helmet sizes, corresponding to a roughly spherical volume 4, 8, 14, or 18 mm in diameter. At the conclusion of treatment, the stereotactic frame is removed and most patients are then discharged. Thus Gamma Knife radiosurgery is most commonly performed on an outpatient basis.

Gamma Knife radiosurgery has shown rapidly increasing acceptance, since the first commercial unit was introduced at the University of Pittsburgh in 1987 (1). Despite the high purchase price (a little >$3 million) and single purpose, Gamma Knife units are widely available in the United States, Europe, Asia, and other parts of the world. All units are manufactured by Elekta Instruments, of Stockholm, Sweden. Use of this device can eliminate the need for open surgery of the brain. Modern surgical techniques and nursing follow-up have reduced the death rate due to brain surgery from as much as 50% in the 1930s to <1% in the United States in 2002. However, Gamma Knife patients most commonly do not have to remain overnight in the hospital at all (an important consideration in a very cost conscious healthcare environment), while craniotomy patients typically have a 2–5 day stay. Conventional brain surgery patients sometimes require 30 days or more of hospitalization if extremely adverse effects occur. Thus, the cost of the Gamma Knife outpatient procedure is typically far less than that for inpatient open brain surgery. Recovery of the patient is much more rapid for Gamma Knife patients, with most patients going home immediately and returning to work or other normal routines in 1–2 days.

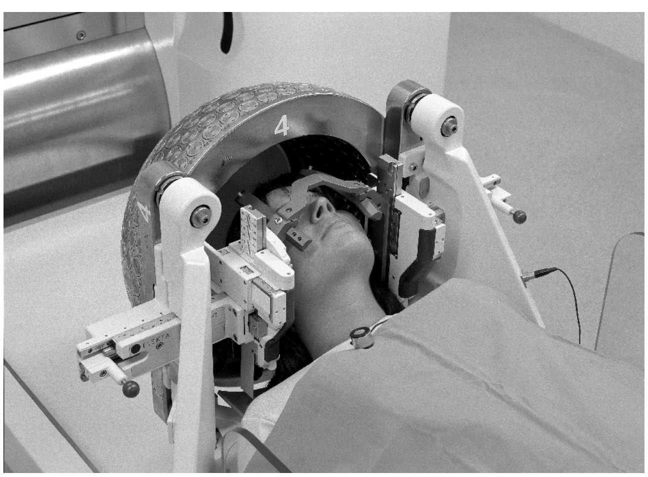

Figure 4. Supine patient in position for treatment in Gamma Knife. Stereotactic head frame is carefully docked with trunnions, which slide in precise channels in the secondary collimator helmet.

EARLY HISTORY OF THE DEVICE

Gamma Knife radiosurgery was an outgrowth of several prior inventions. Dr. Lars Leksell, a Swedish neurosurgeon, was one of the pioneers in the field of stereotaxis (see the article on Stereotactic Surgery). Dr. Leksell was motivated to find minimally invasive ways to treat brain abnormalities by the appalling death rate for early twentieth century brain surgery, which could be as high as 50% (2). Leksell was one of the first surgeons to create a workable stereotactic frame (in 1949) that could be affixed to a patients skull, together with a set of indexed external markers (called fiducials) that were visible on an X-ray of the patient's head. Only primitive brain imaging procedures were available in 1950 to the late 1970s, so stereotactic surgery patients had to undergo a painful procedure called pneumoencephalography. A lumbar puncture was used to introduce air into the spinal canal while the patient (strapped into a special harness) was manipulated upside down, back and forth, while air was injected under positive pressure to displace the cerebro-spinal fluid in the ventricles of the brain. A pair of plane orthogonal X-ray images (anterior–posterior and lateral) were then taken. Since the air-filled ventricles were well imaged by this technique, standard atlases of the human brain such as Schaltenbrand and Wahren (3) were then used to compute the location of the desired target relative to these landmarks. The imaging procedure alone was considered extremely painful and typically required hospitalization. The early stereotactic frames were applied by drilling into the patient's skull and driving screws into the calvarium (outer table of the skull), which was then topped with a Plaster of Paris cap that could be rigidly fixed. A twist drill could then be guided to create a small hole (a few millimeters in diameter) in the patient's skull, through which a catheter could be passed to a designated target, such as the globus pallidum for treatment of Parkinsons disease. A radio frequency transmitter was passed through the catheter and a small volume of tissue was heated to high temperature, creating a deliberate, controlled brain lesion. This procedure, though rigorous, was far less invasive and dangerous than open brain surgery, called craniotomy.

Leksell then attached an X-ray treatment unit to his stereotactic frame and used it in 1951 to treat brain structures without opening of the skull. He called this procedure "radiosurgery", which he defined as "a single high dose of radiation stereotactically directed to an intracranial region of interest" (4). Leksell was successfully in treating previously intractable cases of trigeminal neuralgia, an extremely painful facial nerve disease, by stereotactically irradiating the very narrow ($\sim$ 2–4 mm diameter) nerve as it enters the brainstem. Only a few patients were treated with this X-ray unit.

Leksell then collaborated with physicist Borge Larsson in treating patients at a cyclotron located at Uppsala University near Stockholm beginning in 1957. Tobias and others had just begun treating patients with proton therapy (see article on Proton Beam Radiotherapy) at the University of California Berkeley in 1954. The proton is a positively charged subatomic particle, a basic building block of matter, which has extremely useful properties for treatment of human patients. The charged particles, accelerated to very high energies by a massive cyclotron (typically located at a high energy physics research laboratory) are directed at a patient, where they begin to interact through the Coulomb force while passing through tissue. At the end of the proton range, however, the particles give off a large burst of energy (the Bragg peak) and then stop abruptly. Leksell and Larsson utilized these properties with well-collimated beams of protons directed at intracranial targets. A few other centers in the United States and Russia also began proton therapy in the 1950s and 1960s.

The Gamma Knife was invented in Stockholm, Sweden by Leksell and Larsson and was manufactured (as a prototype) by the Swedish shipbuilding firm Mottola. The first unit had 179 radioactive cobalt-60 sources and was installed in 1968 at Sophiahemmet Hospital in Stockholm, Sweden (5). This original unit had three interchangeable helmets with elliptically shaped collimators of maximum diameter 4, 8, or 14 mm. Despite the lack of good brain imaging techniques at that time, the Gamma Knife was used to successfully treat Parkinson's disease (a movement disorder), trigeminal neuralgia (extreme facial pain), and arteriovenous malformations (AVMs), which are a tangle of congenitally malformed arteries and veins inside the brain. Several years later a second nearly identical unit was manufactured for Leksell when he became a faculty member at Karolinska Hospital in Stockholm. The original unit lay idle for a number of years, until it was donated to UCLA Medical Center in Los Angeles, where it was moved in 1982 (Fig. 5). It was used in animal research and treated a limited number of human patients before it was retired permanently in 1988 (6). The two original, custom-made Gamma Knife units were unique in the world and did not immediately enjoy widespread acceptance or gain much notice. A large number of patients with AVMs began to be treated at the Gamma Knife Center in Karolinska, by Dr. Ladislau Steiner, a neurosurgical colleague of Lars Leksell. Arteriovenous malformations are prone to spontaneous hemorrhage that can cause sudden coma or death. Open surgical techniques for removal of these life-threatening vascular anomalies were extremely difficult and dangerous in the 1970s. Patients came from all over the world to be treated for these AVMs at the Gamma Knife Center in Stockholm.

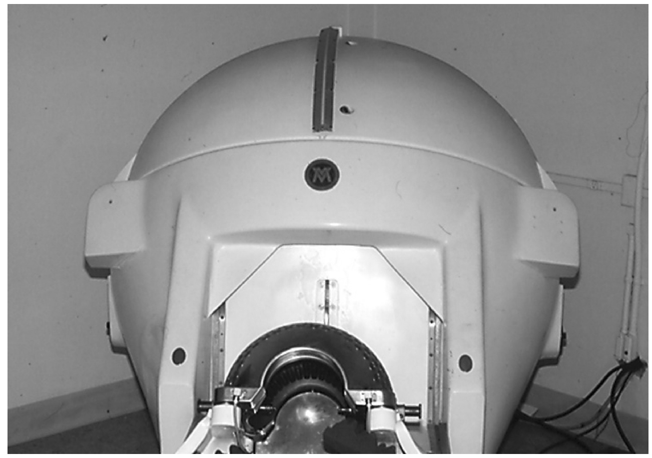

Figure 5. Original Gamma Knife, after being moved from Stockholm to UCLA Medical Center in Los Angeles.

In 1984 and 1985, two new Gamma Knife units were manufactured using Dr. Leksell's specifications by Nucletec SA of Switzerland (a subsidiary of Scanditronix AB, Sweden) for installation in hospitals in Buenos Aires, Argentina and Sheffield, England, respectively (7,8). These units also had three sets of collimators, which were now circular in shape, of 4, 8, and 14 mm diameter, but the number of cobalt-60 sources was increased to 201. The mechanical tolerance was exquisite: The convergence of all 201 beams at the focal point was specified as $\pm$ 0.1 mm. The total radioactivity was 209 TBq (5500 Ci) and the sources were distributed evenly over a $160 \times 60^{\circ}$ sector of the hemispherical secondary collimators (Fig. 6). An ionization chamber (a type of radiation detector) placed at the center of a spherical phantom 16 cm in diameter was used to measure an absorbed dose rate of $\sim$ 2.5 gray $\cdot$ min^{-1} for the Sheffield unit. This was adequate to treat patients to a large radiation dose in a reasonable period of time. Both Gamma Knife units were successfully used fo many years to treat patients in their respective countries.

A new corporation, called Elekta Instruments, AB, of Stockholm was created in 1972 by Laurent and Dan Leksell, sons of Lars Leksell, to manufacture neurosurgical products, including the Gamma Knife, which is now a trademark of this firm. Elekta created the first commercial Gamma Knife product, the Model U, and has manufactured all Gamma Knife units worldwide since that time. This new 201 source unit was installed at the University of Pittsburgh in 1987 and expanded the available beam diameters to include a fourth secondary collimator with a nominal diameter of 18 mm (1). The trunnions, which connect the secondary collimator helmets to the patient, were now configured to dock with connecting points located

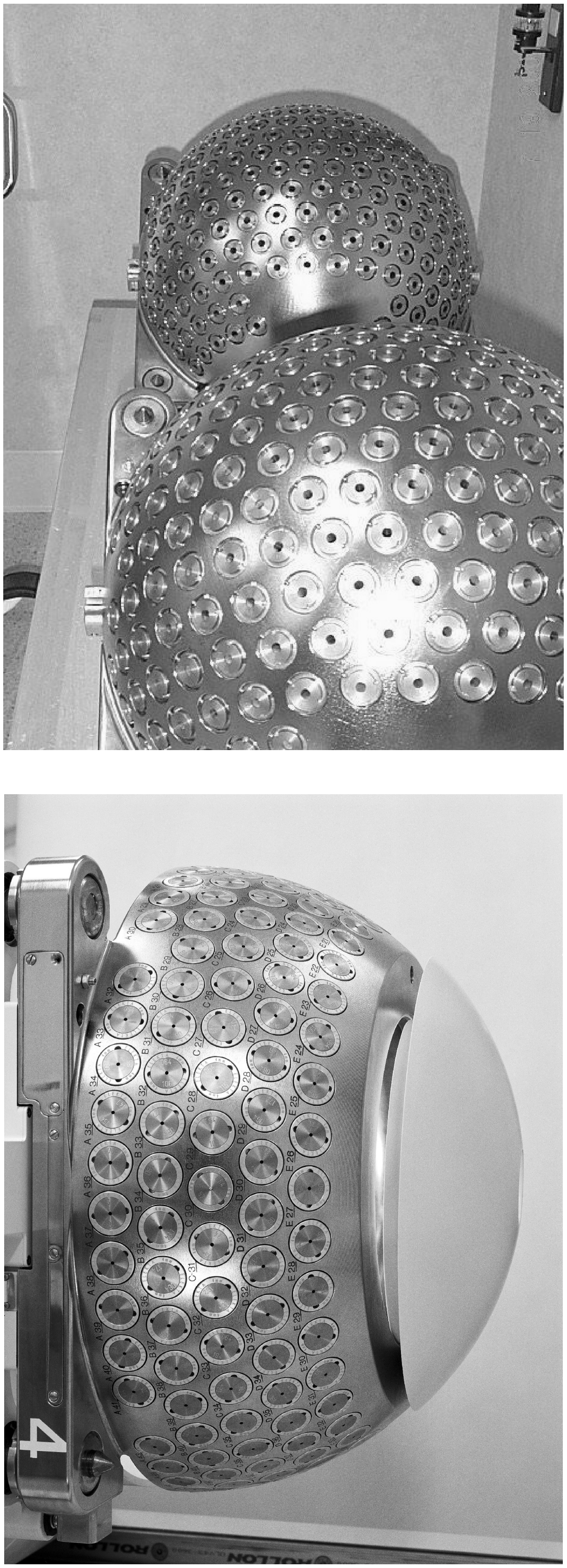

Figure 6. (Upper panel) Collimator helmets for Leksell Gamma Unit Model U. (Lower panel) Collimator helmet for Leksell Gamma Unit Models B and C.

on removable *Y–Z* positioning bars on the patients headframe. The earliest versions of the Gamma Knife had required implantation of screws into the patients skull and covering with Plaster of Paris to achieve this docking. The unit (like the two previous units) utilized a hydraulic drive to open the shielding door in the central body and propel the patient couch into treatment position.

Elekta also introduced a radiation therapy treatment plan called KULA to calculate the size and shape of the radiation volume to be treated for each patient and compute the necessary duration of the treatment. The Sophiahemmet and Karolinska Gamma Knife Centers had relied on manual calculations until this time. The KULA plan could calculate isodose lines (lines of equal radiation dose) in a two-dimensional (2D) plane, which could then be manually traced onto an axial brain image. The advent of stereotactic imaging with computed tomography also eliminated the need for the difficult and painful pneumoencephalograms and was capable of localizing brain tumors as well as anatomical targets. The University of Pittsburgh Gamma Knife Center enjoyed a relatively high degree of acceptance from the time of installation, and was soon joined by other Leksell Gamma Units in the United States, Europe, and Asia.

One drawback of the Leksell Gamma Unit Model U, which is no longer manufactured, is that it was shipped to the hospital unloaded and then loaded with cobalt-60 sources on site. This necessitated the shipment of many tons of shielding materials to create a temporary hot cell, complete with remote manipulating arms (Fig. 7). A further difficulty with Gamma Units is that the radioactive cobalt-60 is constantly being depleted by radioactive decay. The half-life is cobalt-60 is $\sim$ 5.26 years, which means that the radiation dose rate decreases $\sim$ 1%/month. The Sheffield Gamma Unit (manufactured by Nucletec) was reloaded after a number of years of use by British contractors who had not been involved in designing or building the unit and it therefore took $\sim$ 12 months to complete the task. The University of Virginia Leksell Model U Gamma Unit was the first to be reloaded (in 1995) and it was out of service for only 3 weeks. Nevertheless, the necessity of having the treatment unit down for a period of weeks after 5–6 years of operation, at a cost approaching $500,000 with a very elaborate construction scenario inhibited the early acceptance of these units. A compensating advantage of the Gamma Unit Model U was the extremely high reliability of these devices. Routine maintenance is required once every 6 months and mechanical or electrical breakdowns preventing use of the device are very rare.

Leksell introduced the Gamma Unit Model B in Europe in 1988, although it was not licensed in the United States until 5 years later. The new unit, which strongly resembles the later Model C (Fig. 8), departed from the unique spherical shape of the earlier unit and more closely resembled the appearance of a CT scanner. The source configuration was changed to five concentric rings (Fig. 6b), although the number and activity of the cobalt-60 sources remained the same as in the Model U. The new Gamma Unit Model B was designed so that the radioactive cobalt-60 sources could be loaded and unloaded by means of a special

Figure 7. Loading cobalt-60 sources into Gamma Unit with remote manipulating arms.

11 ton loading device (Fig. 9), without the necessity for creating a large and costly hot cell. This significantly reduced installation and source replenishment costs and speeded up these operations as well. The hydraulic operating system used to open the shielding doors and to move the patient treatment couch was replaced with a very quiet electrically powered system.

Extensive innovations were introduced with the Leksell Gamma Unit Model C with optional Automatic Positioning System (APS) in calendar year 2000. This unit was awarded three American patents and one Swedish patent. The new unit provided several upgrades at once: a new computer control system operates the shielding door and patient transport mechanism and is networked via RS232C protocol with the Leksell GammaPlan treatment planning computer. All previous models required manual setting (and verification) of helmet size, stereotactic coordinates and treatment time for each shot. An optional APS system (Fig. 10) has motorized trunnions that permit the patient to be moved from one treatment isocenter to another without human intervention. This automated system can only be utilized if the secondary helmet, gamma angle (angle of patients stereotactic frame Z axis with respect to the longitudinal axis of symmetry of the Gamma Unit helmet) and patient position (prone or supine) are identical to the values for these respective treatment parameters as provided in the final approved treatment plan. In addition, the isocenters (or shots) are grouped into "runs" having stereotactic coordinates within a predefined distance of each other (typically ±2 cm) so as not to introduce unacceptable strain on the patient's neck while their head is being moved

Figure 8. Leksell Gamma Unit Model C, which strongly resembles the previous Leksell Gamma Unit Model B.

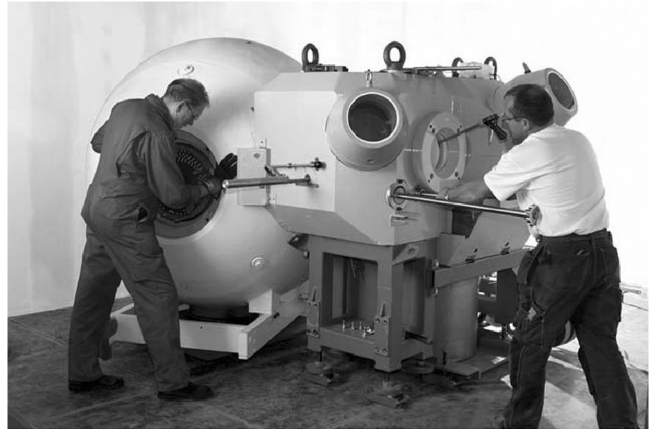

Figure 9. Special loading device for insertion and removal of cobalt-60 sources with the Leksell Gamma Units Models B and C.

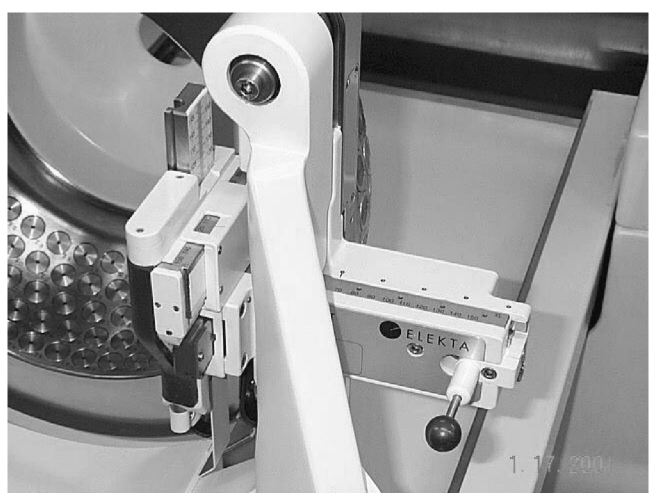

Figure 10. Close-up view of trunnions and helmet of Leksell Gamma Unit model C with Automatic Positioning System in place.

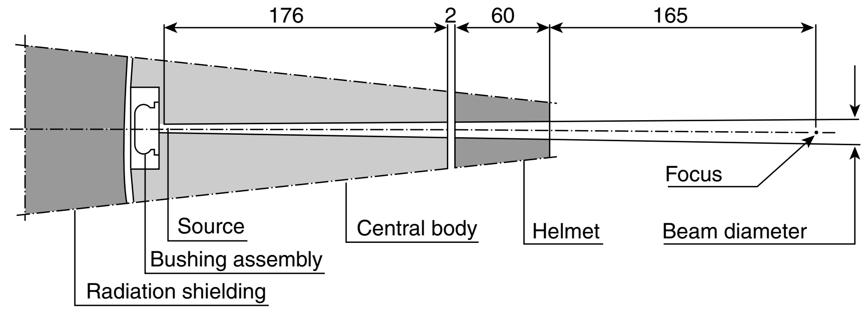

Figure 11. Geometry of sources installed in Leksell Gamma Units.

to a new position relative to the immobile body. Within these limitations the efficiency of a complex treatment plan can be greatly increased. Additionally, two independent electromechanical devices verify the positioning of the patient's stereotactic coordinates to within 50 μm (below the resolution of the unaided human eye).

THEORY

The invention of the Gamma Knife built on seven decades of previous experience with radiation therapy (see related articles). Early external beam radiation treatments used X-ray sets with low energies, in the range of 100–300 kV, which have the disadvantage of depositing a maximum dose at the surface of the skin. This physical characteristic makes it difficult to treat deep seated tumors without causing unacceptable damage to the overlying skin and tissue. Lars Leksell used a 200 kV X-ray set to treat his first radiosurgery patient in 1951, but abandoned that technique after only a few patients to work with far more penetrating proton beam radiotherapy (see article Proton beam radiotherapy). The disadvantage of proton beam therapy was that the patient had to be brought to a high energy physics laboratory, which was not otherwise equipped to treat sick or infirm patients and was often located at a great distance from the surgeon's hospital. This made treatments somewhat difficult and awkward, and the cyclotron was not always available. An important breakthrough came when two Canadian cancer centers introduced cobalt-60 teletherapy (see article Cobalt-60 units for radiotherapy) in the early 1950s. Leksell and Larsson realized that this new, more powerful radiation source could be utilized in a hospital setting. They also realized that rotational therapy, where a radiation source is revolved around a patient's tumor to spread out the surface dose, could be mimicked in this new device by creating a static hemispherical array of smaller radiation sources. Since Leksell was interested only in treating intracranial disease, where the maximum patient dimension is only ~ 16 cm, the device could place radiation sources relatively close to the center of focus. The Leksell Gamma Knife uses a 40 cm Source to Surface Distance (SSD), far shorter than modern linear accelerators (see article Medical linear accelerator), which typically rotate around an isocenter at a distance of 100 cm (see Fig. 11). This short SSD allows the manufacturer to take advantage of the inverse square principle, which implies that a nominal 30-curie source at 40 cm achieves the same dose rate at the focus as a 187.5 curie source would achieve at 100 cm. This makes loading and shielding a Gamma Knife practical.

The Gamma Knife treats intracranial tumors or other targets by linear superposition of 201 radiation beams. The convergence accuracy of these sources is remarkable: The radiation focus of the beams converge at the center point of stereotactic space (e.g., 100, 100, 100 in Leksell coordinates) to within < 0.3 mm. Thus the targeting accuracy of treatment of brain tumors is essentially not limited at all by mechanical factors, and is primarily limited by the inaccuracy of imaging techniques and by target definition. Each cobalt-60 beam interacts by ionization and excitation (primarily by Compton scattering) as it passes through the skull of the patient. The intensity of each beam is diminished by ~ 65% while passing through 16 cm of tissue (a typical skull width, approximated as water for purposes of calculation). At the mechanical intersection of all 201 radiation sources, which are collimated to be 18, 14, 8, or 4 mm in diameter, the useful treatment volume is formed (see Fig. 12). Outside this volume the radiation dose rate drops off precipitously (90% of Full Maximum to 50% in 1 mm for the 4 mm beam) thereby mimicking the behavior of protons at the end of their range. The mathematics of this 3D convergent therapeutic beam irradiation

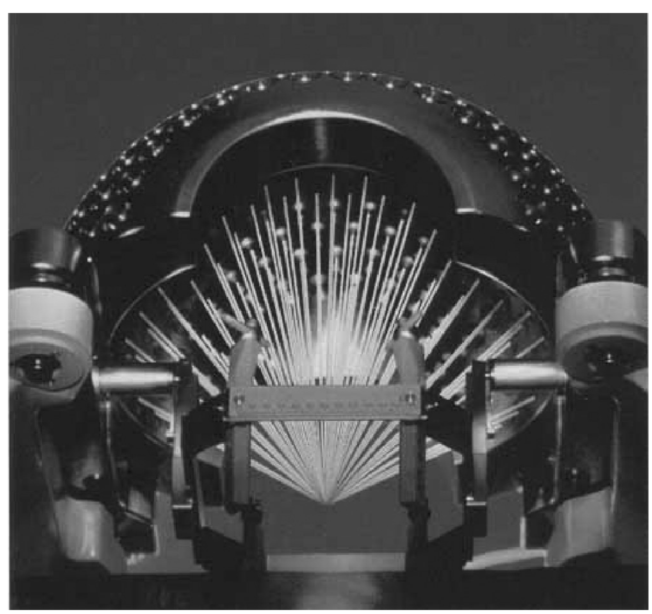

Figure 12. Illustration of convergence of 201 radiation beams to create treatment volume.

is relatively simple: The radiation absorbed dose adds up in linear superposition.

$$D(P) = D_{\text{fi}} / \sum D_{\text{fi}} \times [d_{\text{fs}}/(d_{\text{fs}} - dz)]^2 \times \mu dz$$

where $D(P)$ is the total dose at arbitrary point P, D_{fi} is the relative contribution from source i to the total dose at the point of focus, d_{fs} is the distance from the source to the focus (40 cm), dz is the distance along the beam axis from the focal point to intersection with the perpendicular from point P, and μ is the linear attenuation coefficient for Co-60 gamma radiation in tissue.

A radiation therapy treatment planning code (see article Radiation Therapy Treatment Planning) called Leksell GammaPlan is provided by the manufacturer for the purpose of preparing treatment plans for the Leksell Gamma Unit for use with human patients. An early treatment plan called KULA calculated treatment time and created a 2D plot of lines of equal radiation dose (or isodose lines), but with severe limitations. The early code could only calculate plans with a single center of irradiation (called an isocenter in general radiosurgery applications, or a "shot" in Gamma Knife usage). Calculated isodose lines had to be transferred by hand from a plot to a single CT slice in the axial plane. In 1991 the Leksell GammaPlan software was introduced (and premarket clearance by the FDA was obtained), which permitted on-screen visualization of isodose lines in multiple CT slices. The improved code could calculate and display the results of multiple shots and could model the effect of "plugging" some of the 201 source channels with thick steel plugs to "turn off" certain radiation sources. The software was written for UNIX workstations and has rapidly become increasingly powerful and much more rapid as processing speed and computer memory increased in the last decade. Leksell GammaPlan utilizes a matrix of $> 27{,}000$ equally spaced points (in the shape of a cube), which can be varied from 2.5 cm on a side to 7.5 cm on a side. Within this cube a maximum radiation dose is computed from the linear superposition of all 201 radiation beams (some of which may be plugged), from collimator helmets of 18, 14, 8, or 4 mm diameter, and this calculation is integrated over each "shot". More than 30 different shots (each with a discrete X, Y, and Z stereotactic coordinate, in 0.1 mm increments) can be computed and integrated, with user selectable relative weighting of each shot. Whereas the original KULA plan required ~ 15 min for one single shot calculation, modern workstations with Leksell GammaPlan can now compute 30 shot plans in up to 36 axial slices in < 1 min. Leksell GammaPlan can now utilize stereotactic CT, MRI, and Angiographic studies in the planning process. Each study must be acquired with the stereotactic frame in place and registered separately. Image fusion is now available. Figures 13 and 14 give two of the many possible screen presentations possible with a very sophisticated Graphical User Interface.

CLINICAL USE OF GAMMA KNIFE

The Gamma Knife has gained widespread acceptance in the neurosurgical and radiation oncology community as an effective treatment for many different pathologies of brain tumors, neurovascular abnormalities and functional disorders. Gamma Knife radiosurgery may in some cases be used as an alternative to open craniotomy while for other patients it may be used after previous surgeries have been attempted. Since Gamma Knife radiosurgery infrequently requires overnight hospitalization, and generally has a very low probability of adverse side effects, it may in many cases be much less costly, with lower chance of complication and much less arduous recovery.

A typical Gamma Knife procedure is performed after a patient has been carefully screened by a neurosurgeon, a radiation oncologist, and a neuroradiologist. The procedure is scheduled as an elective outpatient procedure and typically lasts from 3 to 8 h. The first critical step is placement of a stereotactic frame (see article Stereotactic Surgery) to provide rigid patient fixation and to allow stereotactic imaging to be performed with special fiducial attachments. The exact position of the frame (offset to left or right, anterior or posterior) is crucial, since the tumor must be well centered in stereotactic space to permit

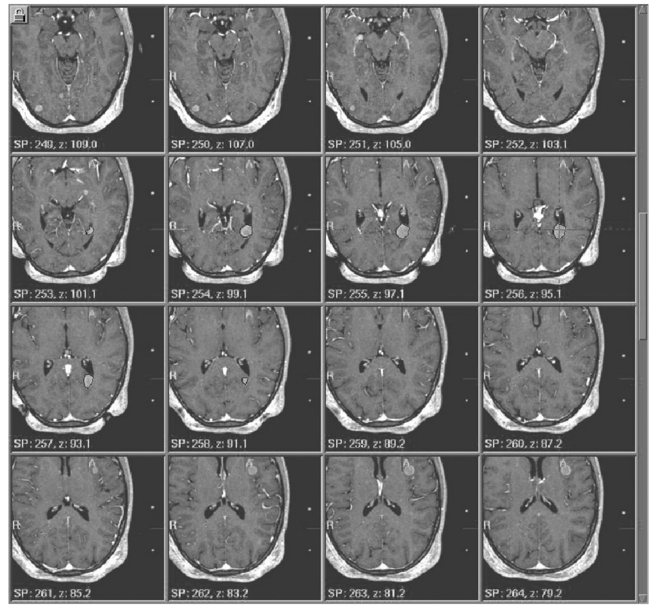

Figure 13. Screen from Leksell GammaPlan illustrating multiple MRI slices with superimposed isodose display.

Figure 14. Screen from Leksell GammaPlan illustrating angiographic study and three-dimensional display of AVM nidus.

accommodation of the patient's skull (with the frame attached) inside the small volume of the secondary collimator helmet. The Leksell Model G frame encloses $\sim 2900\ cm^3$ of accessible stereotactic space, significantly less than other stereotactic frames which do not have to fit inside the Gamma Knife helmet. A stereotactic localization study is immediately performed, using one or more modalities such as computed tomography, and magnetic resonance imaging. Patients with vascular abnormalities may also undergo an angiographic study: A radiologist inserts a thin catheter (wire) into a vein in the patient's groin and then carefully advances the wire up through one of the major arteries leading to the brain, then into the area of interest. The catheter is then used to inject X-ray opaque dye, which reveals the extent of the vascular lesion (see Fig. 14). These imaging studies must then be promptly networked (via a hospital PACS system) to the planning computer. There the images are registered from couch coordinates (left-right, in-out, up-down) to stereotactic space (X, Y, and Z). At that point, each individual point in the brain corresponds to a specific stereotactic coordinate, which can be identified from outside the brain.

Gamma Knife radiosurgery, both in the United States and worldwide, has enjoyed a very rapid acceptance since the first commercial unit was produced in 1987. The number of procedures performed annually, subdivided by indication, is compiled by the nonprofit Leksell Society. Only results voluntarily reported by Gamma Knife centers are tallied, with no allowance for nonreporting centers, so their statistics are conservative. The growth in use of this device has been explosive, with < 7000 patients treated worldwide by 1991 and $> 297{,}000$ patients reported treated through December, 2004 (see Fig. 15). This parallels the increase in number of installed Leksell Gamma units, going from 17 in 1994 in the United States to 96 centers by the end of 2004. The number of Gamma Knife cases reported performed in the United States has increased by an average of 17%/year for the last 10 years, a remarkable increase. Table 1 indicates the cumulative number of patients treated with Gamma Knife radiosurgery in the western hemisphere and worldwide through December, 2004, subdivided by diagnosis.

Treatment objectives for Gamma Knife patients vary with the diagnosis. The most common indication for treatment is metastatic cancer to the brain. An estimated 1,334,000 cancers (not including skin cancers) were diagnosed in the United States in calendar year 2004. Approximately 20–30% of those patients will ultimately develop metastatic tumors in the brain, which spread from the primary site. These patients have a survival time (if not treated) of 6–8 weeks. The treatment objective with such patients is to palliate their symptoms and stop the growth of known brain tumors, thereby extending lifespan. A recent analysis (9) reported a median survival of patients treated with radiosurgery of 10.7 months, a substantial improvement. Approximately 18,000 patients were diagnosed with primary malignant brain tumors in the United States in calendar year 2004, with 13,000 deaths from this cause. Patients with primary malignant brain tumors (i.e., those originating in the brain) have a lifespan prognosis varying from 6 months to many years, depending on the grade of the pathology. Many glioma patients are offered cytoreductive brain surgery to debulk the tumor and may have an extended period of recovery and significant loss of quality of life afterwards. At time of tumor recurrence for these patients, the noninvasive Gamma Knife procedure may accomplish as much as a second surgery, while sparing the patient the debilitation of such a procedure. Recent reports in the clinical literature indicate that Gamma Knife radiosurgery is effective in improving survival for glioma patients.

Many patients with nonmalignant brain tumors are also treated with Gamma Knife radiosurgery. Meningiomas are the most common nonmalignant brain tumor, arising from the meninges (lining of the brain) as pathologically altered cells and causing neurological impairment or even death. Approximately 7000 new meningiomas are diagnosed in the United States each year. Most grow very slowly ($\sim 1\ mm \cdot year^{-1}$) while the most aggressive tumors may grow rapidly to as much as 12–15 cm in length and may even invade the bone. Gamma Knife radiosurgery has been reported for treatment of meningioma as far back as 1987 and is considered a well-established treatment for this extremely persistent disease, with > 1000 Gamma Knife treatments reported for meningioma in the United States during calendar year 2001. Another common nonmalignant tumor is the acoustic neuroma (also called vestibular schwannoma), which arises from the auditory nerve

Table 1. Cumulative Reported Gamma Knife Radiosurgery Procedures through December, 2004

Indication	Western Hemisphere Procedures	Worldwide Procedures
AVM and other vascular	9,793	43,789
Acoustic neuroma	7,719	28,306
Meningioma	11,016	36,602
Pituitary adenoma	3,577	24,604
Other benign tumors	3,137	14,884
Metastatic brain tumors	29,285	100,098
Glial tumors	7,727	20,614
Other malignant tumors	1,501	6,492
Trigeminal neuralgia	11,609	17,799
Other functional disease	1,135	4,441
TOTAL INDICATIONS:	***67,336***	***297,529***

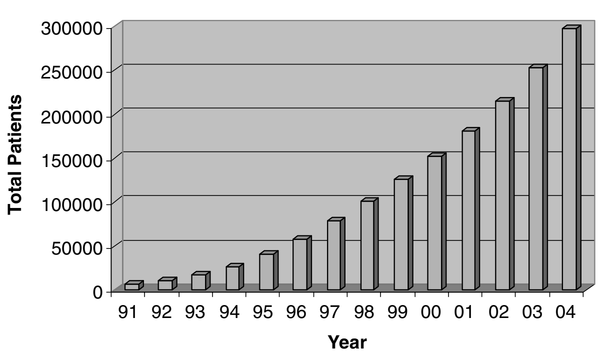

Figure 15. Cumulative number of Gamma Knife patients treated worldwide from 1991 through December, 2004.

(cranial nerve VIII). It can cause deafness and imbalance, and in severe cases motor impairment as it compresses the brainstem. The incidence of newly diagnosed acoustic neuromas is 2500–3000/year in the United States. Craniotomy for acoustic neuroma is among the most challenging brain operations, typically requiring 8–24 h on the operating table. Potential complications range from loss of residual hearing to devastating facial palsy to cerebrospinal fluid leak requiring as much as 30 days of hospitalization. Extremely high control rates of up to 97% (no additional tumor growth or moderate shrinkage) have been reported for Gamma Knife radiosurgery of these tumors with extremely low complication rates (10). This may explain why >1000 acoustic neuromas were treated with Gamma Knife radiosurgery in the United States during Calendar Year 2003, nearly one-third of all such tumors diagnosed that year.

Arteriovenous malformations are a rare genetic disorder of the vascular system of the brain and spinal cord. Estimates of incidence ranges from 5 to > 600/100,000 people. The lesion consists of a tangle of abnormal arteries and veins that may not be detected until late in life. The AVMs can cause debilitating headaches, epileptic seizures, coma, and even sudden death due to cerebral hemorrhage. Arteriovenous malformations were first described in the 1800s and the first surgical resection was credited to Olivecrona in Stockholm in 1932. The AVMs were categorized by Spetzler and Martin into five distinct surgical categories in order of increasing surgical risk and one additional category for inoperable lesions (11). Surgery for these lesions remained extremely challenging until late in the twentieth Century. Therefore, when angiography became available in the 1960s, Ladislau Steiner (a neurosurgical colleague of Lars Leksell at Karolinska Hospital) began to treat AVMs with the Gamma Knife as early as 1970 (12). A large number of AVMs were treated in the early days of Gamma Knife radiosurgery both because of the extreme risk of open surgery and the early success with this technique in obliterating these lesions. Recent clinical studies report an obliteration rate for these lesions of 75–85% within 3 years of Gamma Knife radiosurgery, with similar obliteration rates if a second Gamma Knife treatment is necessary. Over 33,000 AVMs have been treated with Gamma Knife radiosurgery worldwide, making it the second most common indication after metastatic brain tumors.

Trigeminal neuralgia is a neurological condition marked by excruciating pain of the fifth cranial nerve that enervates the face in three branches between the eyebrows and the jawline. The pain may be caused by a blood vessel pressing on a nerve, by a tumor, by multiple sclerosis, or for unknown reasons. This is the first condition ever treated by Lars Leksell, using a 200 kVp X-ray unit affixed to a stereotactic frame in a treatment performed in 1951. The root entry zone of the nerve as it enters the brainstem is the target volume. The nerve diameter at that point is only 2–4 mm and the consequences of a geometric miss with the radiosurgery treatment volume accidentally being directed to the brainstem could be quite severe. Alternative treatments include injection of glycerol into the cistern under radiographic guidance, radio frequency "burn" of the nerve under radiographic guidance and microvascular decompression which is a fairly major brain surgery. Physicians at the University of Pittsburgh recently reviewed their first 10 years of treatments on 202 trigeminal neuralgia patients and found that > 85% had complete or partial relief of pain at 12 months after Gamma Knife radiosurgery (13). Over 12,500 patients with trigeminal neuralgia have been treated with Gamma Knife radiosurgery at this writing.

QUALITY CONTROL/QUALITY ASSURANCE

Quality Control and Quality Assurance for Gamma Knife radiosurgery is of critical importance. Unlike fractionated radiation therapy, Gamma Knife treatments are administered at one time, with the full therapeutic effect expected to occur in weeks, months, or years. Errors in any part of the radiosurgery process, from imaging to planning to the treatment itself could potentially have severe or even fatal consequences to the patient. An international group of medical physicists published a special task group report on Quality Assurance in stereotactic radiosurgery in 1995 (14) and the American Association of Physicists in Medicine discussed Quality Assurance for Gamma Knife radiosurgery in a task group report in that same year (15). Each group stressed the need for both routine Quality Control on a monthly basis, examining all physical aspects of the device, and calibration of radiation absorbed dose measurements with traceability to national standards. Both groups also emphasized detailed documentation and independent verification of all treatment parameters for each proposed isocenter before the patient is treated. An Information Notice was published by the U.S. Nuclear Regulatory Commission (NRC) on December 18, 2000 that documented 16 misadministrations in Leksell Gamma Knife radiosurgery cases in the United States over a 10-year period (16). The Nuclear Regulatory Commission defines a misadministration as "A gamma stereotactic radiosurgery radiation dose: (*1*) Involving the wrong individual, or wrong treatment site; or (*2*) When the calculated total administered dose differs from the total prescribed dose by > 10% of the total prescribed dose." Fifteen of the 16 incidences were ascribed to human error while utilizing the Leksell Gamma Knife models U, B, and B2. Six of the reported errors involved setting incorrect stereotactic coordinates (often interchanging *Y* and *Z* coordinates). Two errors occurred when the same shot was inadvertently treated twice. One error involved interchanging left and right side of the brain. One error involved using the wrong helmet. No consequences to patients were reported, but would be expected to be minor in most of the reported cases.

It is important to note in this respect that the new Leksell Gamma Unit Model C with (optional) Automatic Positioning System has the potential to eliminate many of the reported misadministrations. The older Leksell Gamma Unit Models U and B are manual systems in which the treatment plan is printed out and hand carried to the treatment unit. Stereotactic coordinates for each of the isocenters (shots) are set manually by one clinician and checked by a second person. It is thus possible to treat the patient with the wrong helmet, prone instead of supine, wrong gamma angle, incorrect plugged shot pattern, wrong time, or to repeat or omit shots. The operation of the new Model C Gamma Unit is computer controlled. The Leksell GammaPlan workstation is networked via an RS232C protocol with full error checking, thus transferring the treatment plan electronically. The shots may be treated in any order, but no shot may be repeated and the screen will indicate shots remaining to be treated. The helmet size is remotely sensed and treatment cannot commence if an incorrect helmet is selected. If the optional Automatic Positioning System is used, the X, Y, and Z stereotactic coordinates are automatically sensed to within 0.05 mm. The device will not permit treatment until the X, Y, and Z coordinates sensed by the APS system match those indicated on the treatment plan. Thus, it appears that all of the 15 misadministrations due to human error as reported by the Nuclear Regulatory Commission would have been prevented by use of the Model C with APS.

RISK ANALYSIS

The concept of misadministration should be placed in the larger concept of risk analysis. All medical procedures have potential adverse effects and, under state laws, patients must be counseled about potential consequences and sign an informed consent before a medical procedure (even a very minor procedure) may be performed. The relative risk of misadministration of Gamma Knife misadministration may be computed, utilizing the NRC report and data from the Leksell society on number of patients treated per year in the United States. Since $\sim$ 28,000 patients received Gamma Knife radiosurgery between 1987 and 1999, while 16 misadministrations were reported during the same interval, a relative risk of misadministration of 0.00057 per treatment may be computed for that period. Using the most recent year (1999) for which both NRC and patient treatment data are available, the relative risk drops to 0.0001/patient treatment.

These risks may be compared with other risks for patients undergoing an alternative procedure to Gamma Knife radiosurgery, namely, open craniotomy with hospital stay (17). A report by the National Institute of Medicine estimates that medical errors kill between 44,000 and 98,000 patients/year in the United States (18). These deaths reportedly occur in hospitals, day-surgery centers, outpatient clinics, retail pharmacies, nursing homes, and home care settings. The committee report states that the majority of medical errors do not result from individual recklessness, but from basic flaws in the way the health system is organized. A total of 33.6 million hospital admissions occur in the United States each year, which yields a crude risk estimate range of 0.0013–0.0029 death per admission to hospital or outpatient facility.

A second source of inadvertent risk of injury or death must also be considered. The National Center for Infectious Diseases reported in December, 2000 that an estimated 2.1 million nosocomial (hospital based) infections occur in the United States annually (19). These infections are often drug resistant and require extremely powerful antibiotics with additional adverse effects. Given that there are 31 million acute care hospital admissions annually in the United States, the relative risk of a hospital based infection may be computed as 0.063/patient admission, or roughly one chance in 16. The risk of infection from craniotomy was given by the same report as 0.82/100 operations for the time period January, 1992–April, 2000.

The Leksell Gamma Knife Model C system is one example of a computer-controlled irradiation device. The rapidly developing field of Intensity Modulated Radiation Therapy (IMRT) is the subject of a separate article in this work. These complex treatments require extraordinary care on the part of treatment personnel to minimize the possibility of misadministration. Only rigorous Quality Assurance and Continuing Quality Improvement in radiation oncology can make such treatments safe, reliable and effective. Leveson has studied the use of computers to control machinery which could potentially cause human death or injury, such as linear accelerators, nuclear reactors, modern jet aircraft and the space shuttle (20).

EVALUATION

The Leksell Gamma Knife, after a long period as a unique invention of limited applicability, has enjoyed explosive growth in medical application in the last 10 years. It is one of a number of medical instruments specifically created to promote minimally invasive surgery. Such instruments subject human patients to less invasive, painful, and risky procedures, while often enhancing the probability of success or in fact treating surgically inoperable patients. Over 297,000 Gamma Knife treatments have been performed worldwide as of the last tally. Most treatments are successful in achieving treatment objectives in 85–90% of patients treated. Although the Gamma Knife is the most massive and probably the costliest single medical product ever introduced, it has enjoyed widespread commercial and clinical success in 31 countries. The simplicity and reliability of operation of the unit make its use an effective treatment strategy in lesser developed countries where difficult craniotomies may not be as successful as in more developed countries. The newest version of the unit addresses the issues of automation, efficiency, treatment verification, and increased accuracy. The instrument appears to be well established as an important neurosurgical and radiological tool.

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See also COBALT 60 UNITS FOR RADIOTHERAPY; RADIOSURGERY, STEREOTACTIC.