Radiosurgery and Pathological Fundamentals
Radiosurgery and Pathological Fundamentals

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‘I was born under the sign of Sagittarius and I liked the motto: to ride, to shoot with the bow, and to tell the truth.’
Acknowledgement

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Within the past 3 decades, and more precisely within the last 5 years, radiosurgery has become a fundamental arm in neurosurgery.

Starting with arteriovenous malformations, it is currently a basic treatment for grade I and II vestibular schwannomas, cavernous sinus meningiomas, recurrent pituitary tumors, metastases, and recently also for trigeminal neuralgia, temporal lobe epilepsy and other functional neurosurgery indications. A new door has recently been opened for spinal tumors.

But, in spite of a very wide clinical experience, one should recognize the lack of fundamental researches, the need for a better understanding of radiobiology and for more pathological studies. That is one of the major contributions of the monograph edited by G.T. Szeifert, D. Kondziolka, M. Levivier and L.D. Lunsford entitled Radiosurgery and Pathological Fundamentals.

A better understanding of radiobiological processes will enhance the quality of radiosurgery, focus the indications together with new applications.

The sterile fight between conventional microneurosurgery and radiosurgery is behind us. Today, it is clear that both modalities are complementary. But when there is a choice, the best should be offered to the patient, taking into consideration medical treatment, risk of therapy with an ultimate goal – quality of life.

Jacques Brotchi
President of the WFNS
It's been a great pleasure working with Professors Szeifert, Kondziolka and Levivier in the preparation and review of the current Volume 20 of *Progress in Neurological Surgery*. Stereotactic radiosurgery has turned out to be not just a small blip on the great ocean of brain surgery, but in fact a veritable ocean liner. It has had amazing staying power related to its original goal; a minimally invasive low risk strategy designed as an alternative or primary management for difficult tumors, vascular malformations, movement disorders, pain problems, and epilepsy. It has spawned a remarkable re-evaluation of radiobiology, and has emphasized that when done with precision, small volumes of tissue can be inactivated or eradicated using closed skull radiosurgery. What has been missing to a large extent has been a long-term analysis of the mechanisms of the pathologic substrate, as well as better understanding of adverse radiation effects. This is in part related to the successful outcomes that most patients obtain after radiosurgery, which limits the amount of eventual histopathological data. I believe that this volume helps address that question.

Professor Szeifert, perhaps the only neurosurgeon who trained as a neuropathologist (in addition to being a concert organist) is an individual uniquely equipped to be able to lead the team of authors who assembled this monograph. Many of the chapters provide new insights into the field of radiosurgery. Pay special attention to the introductory chapter of my own personal mentor, Professor Erik Olof Backlund. He gives a unique historical summary of the early days of radiosurgery under the guidance of the great Swedish innovative neurosurgeon, Lars Leksell. The timing of this book is also a fitting memorial to the vision and creativity of Professor Leksell who was born in 1907. On the
100th Anniversary of his birth, many surgeons who are first-, second- or third-generation disciples of Leksell assisted in this volume. Lars Leksell envisioned this concept and defined the term stereotactic radiosurgery in 1951. In this half a century, and especially in the last 25 years, the knowledge base of the field of stereotactic radiosurgery has dramatically increased. The procedure has tremendous staying power. At many neurosurgical centers of excellence across the world, it accounts for 10% or more of all intracranial brain surgery being done.

L. Dade Lunsford, MD
In the fall of 1960, a few months after my beginning as a resident of the Department of Neurosurgery at the Karolinska Institute in Stockholm, Lars Leksell came to this Department as the new Professor and Chairman, succeeding Herbert Olivecrona, the founder of Swedish neurosurgery. I became immediately acquainted with Leksell’s on-going and indeed very exciting experiments together with the radiobiologist Börje Larsson in Uppsala, on trying to develop ‘stereotactic radiosurgery’, aimed at lesioning in the central brain in functional operations such as thalamotomy and capsulotomy. Clinical experiments using a proton beam were initiated at the Gustav Werner Institute in Uppsala, and a few patients had been treated [1]. Experiences from these led Leksell to design a multi-source ‘beam knife’, which became ready for use in 1967 [2] as the first ‘Gamma Knife’ (GK). It was financed by nongovernmental funding and installed at the private hospital Sophiahemmet in Stockholm as a clinical research unit to be run by the staff at the Department of Neurosurgery of the Karolinska Institute/Hospital.

The basic concept of the GK was that extremely well-collimated beams from a large number of Cobalt-60 sources, distributed around a half-spherical collimator helmet, would allow a circumscribed focus of beams to be produced in the central part of the patient’s skull. The direction of beams and the placement of this focus should be guaranteed by stereotactic measures. Although the primary aim with the GK was to offer ‘nonsurgical’ lesioning in the central gray for functional surgery, it seemed obvious that it would also offer precision irradiation of small intracranial tumors, e.g. those of the pituitary. This latter concept, using proton beams, had already been exploited at a few other centers in other countries [3–5].
The arrival of the GK did matter a lot to me personally, just leaving behind the final phase of my specialization, to be intimately acquainted with the principle of ‘bloodless surgery’. For example it would enable me to be instrumental in starting new and tentative projects within my own fields of interest, precision irradiation of pituitary tumors in particular. First of all, I eagerly wanted to include the longed for GK alternative in my protocol for stereotactic cranio-pharyngioma treatment. Moreover, I had plans to try a noninvasive/outpatient technique for destruction of the normal pituitary in cases of advanced mammary carcinoma, a current therapeutic principle during the 1960s.

This might explain why I, together with Leksell himself and Börje Larsson in October 1967 came to constitute the first GK operation team in history. The case was one of a series of cranioopharyngiomas, later constituting the case material of my own PhD thesis. The patient was a young man with a cranioopharyngioma where the cystic part had been treated previously by intracavitary irradiation, using Yttrium-90 colloid [6]. The solid tumor remnant was of appropriate size for one single lesion using the smallest (5 × 3 mm) collimator alternative, and 20 Gy were given to the center of the tumor. A plaster of Paris cap (fig. 1), secured to the patient’s skull by three aluminum screws was used as a mechanical interface, allowing the head to be attached to the axis trunnions of the GK in agreement with precalculated stereotactic coordinates. Unexpectedly the patient died from an acute shunt obstruction 4 months later, allowing us to study the radiation effect at autopsy. A small crescent of surviving tumor tissue was found, surrounding a central tumor necrosis [7]. This first case was fol-

**Fig. 1.** The plaster of Paris cap used for the first GK patient in 1967 (now on display at Dade Lunsford’s OR in Pittsburgh, Pa., USA).
followed by a pituitary adenoma patient (see below), a few patients with intractable cancer pain for ‘gamma-thalamotomy’ [8], and another craniopharyngioma patient (summarized data in table 1).

The second case in table 1 (ÖD) was a man who had a ‘chromophobe adenoma’ removed transfrontally by me in 1967. Postoperative irradiation was part of the routine for these tumors at that time. Having the sophisticated GK single-dose technique at our disposal, our oncology colleagues agreed to use that alternative for the irradiation. An arbitrary dose of 28 Gy was given to the center of the sella, the dose level chosen with the regard to the assumed radiation tolerance of the optic pathways. The optic chiasm was assessed to have received less than 5–6 Gy. During a 2-year follow-up, there was radiological evidence of a slight shrinkage of the irradiated volume.

These pilot cases stimulated the GK staff to design virtual research protocols for further systematic studies, and principal investigatorships were defined for each project. For example under my mentorship, the two senior residents Tiit Rähn and Georg Norèn were given personal tasks with pituitary and acoustic tumors, respectively. Over the coming years, these two young colleagues presented reports on patients with Cushing’s disease and vestibular schwannomas treated with the GK, which must be considered seminal, each in its field, for the further progress of radiosurgery [9, 10]. Ladislau Steiner, already in charge of the routine vascular surgery, received the paramount responsibility for the most exciting GK project, the irradiation of intracranial arteriovenous malformations (AVMs). We were all spellbound over the results in the latter, where already in the first tentative cases a marvelous disappearance of the malformation could be seen (fig. 2).

**Table 1.** GK I: the first ten operations

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Irradiation date</th>
<th>Max. dose, Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FE</td>
<td>Craniopharyngioma</td>
<td>October 1967</td>
<td>20</td>
</tr>
<tr>
<td>ÖD</td>
<td>Pituitary adenoma</td>
<td>January 27, 1968</td>
<td>28</td>
</tr>
<tr>
<td>EN</td>
<td>Intractable cancer pain</td>
<td>February 22, 1968</td>
<td>~150</td>
</tr>
<tr>
<td>JO</td>
<td>Intractable cancer pain</td>
<td>February 23, 1968</td>
<td>~150</td>
</tr>
<tr>
<td>WA</td>
<td>Intractable cancer pain</td>
<td>March 27, 1968</td>
<td>~150</td>
</tr>
<tr>
<td>JO2</td>
<td>Intractable cancer pain</td>
<td>April 24, 1968</td>
<td>~150</td>
</tr>
<tr>
<td>BE</td>
<td>Craniopharyngioma</td>
<td>May 21, 1968</td>
<td>50</td>
</tr>
<tr>
<td>BL</td>
<td>Intractable cancer pain</td>
<td>May 29, 1968</td>
<td>~200</td>
</tr>
<tr>
<td>EL</td>
<td>Intractable cancer pain</td>
<td>June 29, 1968</td>
<td>~200</td>
</tr>
</tbody>
</table>
Professor Leksell himself was strongly involved in the treatment of patients with intractable cancer pain, not least to try to develop peroperative pain tests for assessing the expected radiolesions in the nonspecific pain pathways in centrum medianum. Personally, I also foresaw a project on pineal tumors, together with Tiit Rähn, enabling us to avoid, by stereotactic biopsy, the common diagnostic ‘guessing’ in these lesions, after which GK lesioning should be made in suitable, i.e. circumscribed and nonmalignant tumors.

The gradual emergence of tentative scientific reports during the first decade is summarized in table 2.

Table 2. Original papers from the GK I group, 1968–1980

<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1968</td>
<td>Leksell [8]</td>
<td>Gammathalamotomy</td>
</tr>
<tr>
<td>1971</td>
<td>Leksell [12]</td>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td>1972</td>
<td>Steiner et al. [13]</td>
<td>AVM</td>
</tr>
<tr>
<td>1972</td>
<td>Backlund et al. [14]</td>
<td>Pituitary ablation</td>
</tr>
<tr>
<td>1974</td>
<td>Backlund et al. [15]</td>
<td>Pineal tumors</td>
</tr>
<tr>
<td>1978</td>
<td>Thorén et al. [9]</td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>1979</td>
<td>Leksell and Backlund [16]</td>
<td>Gammacapsulotomy</td>
</tr>
</tbody>
</table>

Fig. 2. Radiological findings in one of the first AVM patients. Carotid angiography before (a) and 2 years after GK irradiation (b).
Snapshots

The famous pituitary surgeon Jules Hardy had just postulated that the most common location for ACTH adenomas in Cushing’s syndrome is in the most anterior part of the anterior pituitary lobe. Thus Tiit and I decided, as a first step in a new case, to irradiate this part only, and wait for any hormonal response. To our satisfaction, this seemed to be correct. As many as 48% of those treated with this very limited field only went into remission, and could escape adrenalectomy. Those who did not respond had a second (or third, or even fourth) GK course, for the remaining gland. The overall results from this step-by-step irradiation protocol were very rewarding [9].

Snapshot: Tiit patiently contemplating at the light box, meticulously examining serial X-rays and tomographies of Cushing patients, looking for irregularities of the sellar floor, possibly disclosing the extension and location of the ACTH adenoma. Together with previous pneumoencephalographic findings, any such sellar pathology guided the dose planning. The CT technique was still in the future.

In the AVM patients, there was empirical evidence that the ‘shunting compartment’ of the malformation might be the critical volume for irradiation. Thus, scrutinizing analysis of the angiograms was crucial. But out of the AVM patients admitted, who should be irradiated, and who should not? Of those irradiated, why did some respond well and in a reasonable time, and some not?

Snapshot: Ladislau contemplating for hours in his office, at his light box, discussing preoperatively various collimator alternatives and field configurations with the radiophysicist, and subtle if any changes in early postirradiation angiograms with the neuroradiologist.

Lars Leksell himself actualized important ethical issues. One example: in contrast to the ‘reasonable’ doses given in tumors and AVMs, for capsulotomy very high doses were deemed necessary, performed as they should be in presumably ‘radioresistant’ normal brain tissue. For doses around 150 or 200 Gy, an irradiation time of many hours would then be necessary. It was tempting to divide such a tedious procedure into two parts, with a night in between, thus the first part could serve the purpose of a sham operation. Would that be ethically tolerable?

Snapshot: Lars telling me that after serious consideration he did not find such a two-step operation violating ethical standards, as the intermission (1) would be nothing but extremely relaxing for the patient, and moreover (2) would do no harm whatsoever.

Georg had a less enviable situation in his task to ‘hit’ properly the smaller acoustic tumors selected for the GK. For the dose planning, he had to get the
tumor visualized on the stereotactic X-ray, notably without the possibility to include, in the GK procedure, pneumoencephalography, the common and the only road to radiological diagnosis at that time.

*Snapshot:* The radiologist and Georg climbing around in the X-ray lab, intermittently and quickly turning the patient to head positions optimal for a small amount of positive contrast (intrathecal metrizamide) to be captured on the film.

The main aim of a tentative study in 8 patients with advanced mammary carcinoma was to explore the possibility of halting the disease by ‘gamma-hypophysectomy’. My preliminary impression was that we failed as the pituitary hormonal levels were found essentially unchanged after the GK irradiation, and moreover the cancer continued to ruin the patient’s life.

*Snapshot:* Tiit stubbornly emphasizing – in retrospect and after regretting publication of a preliminary report [14] – that we might not have failed completely, as all the ‘gamma-hypophysectomy’ patients were pain free after the GK treatment. We might have been, without fully appreciating it, on the tracks of the up to that time unknown pituitary-related endorphin system.

**Methodological Progress**

In a historical account like this, it would be unfair not to mention how many of us involved had to solve purely practical/technical problems of joint responsibility related to the irradiation procedure proper. We had the machine, in splendid sophistication, but regarding its practical use, a number of details were less than obvious. A few examples are given here.

(1) **The Attachment**

The dimensions of the collimator helmets of the GK were set from the radiophysical requirements. In principle and ideally, the patient’s head should be placed as close as possible to the radiation sources (i.e. the inner aperture of each of the 198 collimators) to avoid any surplus scattered radiation contributing to an unwanted integral dose. To satisfy this, the space within the collimator helmet had been made very narrow, not allowing any stereotactic frame to be used for the alignment of the patient to the GK. Leksell had foreseen a routine where less space-occupying, individually modeled and disposable fixtures should solve the problem of mechanically securing the patient. As mentioned above, the first patient had a plaster of Paris cap made around his head, secured to the skull by metal screws. Leksell later substituted the plaster of Paris by Thermoplast (fig. 3). Both myself and my younger associates found the ‘cap’ technique less
convenient for the surgeon and indeed unpleasant for the patient. Thus some standardized aluminum interphases, a kind of ‘pseudo-frames’, were designed. An important additional reason to give up the ‘cap’ technique (allowing nothing but a one-isocenter irradiation) was that we wanted eagerly to introduce a multi-target (field cluster) technique for the larger tumors. The ‘pseudo-frames’ worked very well for this purpose, and it was not until the Elekta company introduced the so-called G-frame (for GK II), that the attachment technique was standardized. One of the ‘pseudo-frames’ is shown in figure 4. An example of a cluster irradiation using this frame is shown in figure 5.

(2) Individual Adjustments of Radiation Parameters

For the planning of each individual treatment, it was crucial to know the dimensions and form of the radiation field, as well as the irradiation time necessary for a certain radiation dose. We then profited from the thorough 3-dimensional calculations made during the GK construction work, and used a few standardized, ‘average’ dose diagram templates to superimpose directly upon the diagnostic X-rays. This was a tolerable compromise when it came to single-isocenter irradiations and the small apertures. But as soon as we introduced double- (or multi-) target irradiations, the individual, composite isodose

Fig. 3. Capsulotomy patient in position in GK I, just before attachment to the trunnion axes. The lateral stereotactic coordinate is set on the left axis (by the author, right). In this case, an Orthoplast cap was used. (Research engineer Bengt Jernberg to the left.)
Fig. 4. The standard Leksell stereotactic frame attached outside a ‘pseudo-frame’, designed for cluster irradiations. Guided by the former, a pattern of drill holes (for the axis trunnions) representing the configuration of the dose diagram was made in plexiglass sheets (a) fitting into a ‘box’ on the ‘pseudo-frame’ (b), during the irradiation.

Fig. 5. Cluster irradiation of a giant recurrent pituitary adenoma (in October 1969), using the ‘pseudo-frame’ shown in figure 4. The $3 \times 5$ collimator alternative is used in five isocenters.
diagrams had to be ‘hand-calculated’ and hand-drawn, by the radiophysicist as computed dose planning was still far ahead (fig. 6).

(3) Treatment Nomogram

As the radiation source was Cobalt-60, with a defined decay over time, the operation planning had to take the actual irradiation date into consideration. Although most of the irradiation targets were rather centrally located in the head, the degree of ‘eccentricity’ of the focus (i.e. the average distance from skin to target) moreover influenced the dose rate (and thus the irradiation/exposure’
time) in the individual case. To facilitate such individual adjustments without separate calculations, I designed a smart ‘nomogram’ (fig. 7).

(4) GK – The Second Generation

Lars Leksell’s original and basic idea with the GK was to obtain a new kind of surgical tool for ‘cutting’ in the brain, for tractotomy, thalamotomy, etc. However, the first years with a number of tentative cluster irradiations in the first GK clearly showed the need for a modified, second-generation machine, allowing (more) spherical radiation fields to be produced, using cylindrical collimators. This work for a GK II started immediately. I suggested that two (or three) collimator alternatives should be made, each with the cross-section of the individual cylindrical beam in the target area to be 4, 8 and 14 mm. The latter two alternatives were chosen for the GK II, taken into use in 1974. It was installed at the Karolinska Hospital in Stockholm (fig. 8), where a dedicated radiosurgical OR was built. One year later, when professor Leksell retired, I was appointed to a formal position as Chief of the Stereotactic Service at the Karolinska Hospital, including the GK.

Concluding Reflections

This very comprehensive account, a few personal impressions a bit out of an official record, mirrors a short, intense and indeed exciting decade of
neurosurgical history, initiated by one of the most innovative minds of the neurosurgical community, Lars Leksell. In his absolutely indefatigable creativity, he led his team with steady but generous hands; thus every individual around the first GK was given his particular role and a certain freedom, fostering both self-esteem and responsibility. And we learned, like maybe few other clinicians, to appreciate the indispensable intimate collaboration with people off the clinical floor, radiobiologists, physicists, technicians. We shared each other’s ideas and suggestions in a mode probably not so often seen among tight groups of people in the van.

Notably, moreover, we spontaneously never saw this new field of work as a branch of any ‘radiation therapy’. Indeed, it was natural to look upon it as a branch of surgery, radiosurgery. I have previously published a thorough discussion on the arguments for that [17].

Finally, it must not be forgotten that we saw but few, if any, appreciating glances from the neurosurgical community in the world around, notably not even in Sweden; ‘no one is a prophet in his native city’. Particularly our work was far from recognized as a step forward by influential microsurgeons, who had difficulties to see the potentiality in this new therapeutic concept. To some, the provocative
principle of ‘not removing a tumor but inactivating or obliterating it’ primarily with the aim of minimizing the risk for the patient was even awfully insulting. Being the first of Lars Leksell’s pupils to be involved in the GK project, and presumably being the one most intimately engaged in it during the first few years, indeed I consider myself most privileged, and I have collected these small memoirs with pride but also in great gratitude.

References


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