(25) # The Gamma Knife in ophthalmology. Part one – uveal melanoma

Zastosowanie Gamma Knife w okulistyce. Część pierwsza – czerniak błony naczyniowej

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Summary: The Gamma Knife was designed by Lars Leksell in the early 1950's. It gave rise to a new discipline of medicine – stereotactic radiosurgery. Primarily dedicated to neurosurgery, the Gamma Knife has become an alternative, widely used surgery technique. According to Elekta's statistics, approximately 60,000 people are treated with Leksell Gamma Knife every year and it is the most extensively studied stereotactic radiosurgery system in the world. The Leksell Gamma Knife can also be used in ophthalmology. The gamma ray beam concentration enables effective treatment of uveal melanoma, choroidal hemangioma, orbital tumors or even choroidal neovascularization. The virtue of Leksell Gamma Knife is its extreme precision, non-invasiveness and the possibility of outpatient treatment, which significantly reduces costs and diminishes post-operative complications. Innovative solutions shorten a single session to a minimum, which is very comfortable and safe for both staff and patients. Advantages and possible side effects of gamma knife radiosurgery are well-documented in the professional literature. The objective of this review is to present the recognized applications of Leksell Gamma Knife in ophthalmology.

Key words: Gamma Knife, stereotactic radiosurgery, uveal melanoma, neovascular glaucoma.

Streszczenie: Gamma Knife zaprojektowany w latach 50. minionego stulecia przez Larsa Leksella dał początek nowej dziedzinie zwanej radiochirurgią stereotaktyczną. Chociaż stworzono go z myślą o zastosowaniu w neurochirurgii, z czasem stał się powszechnie używany w pozostałych dziedzinach medycyny – alternatywnie do innych technik chirurgicznych. Zgodnie z doniesieniami firmy Elekta rocznie około 60000 osób jest leczonych za pomocą Gamma Knife, na świecie jest on najlepiej poznanym urządzeniem stosowanym w radiochirurgii stereotaktycznej. Leksell Gamma Knife znalazł zastosowanie również w okulistyce. Wykorzystanie skupiających się wiązek promieniowania jonizującego pozwala na skuteczne leczenie czerniaków błony naczyniowej, naczyniaków naczyniówki, guzów oczodołu, a nawet ognisk neowaskularyzacji naczyniówkowej. Zaletą Leksell Gamma Knife są submilimetrowa precyzja, nieinwazyjność oraz możliwość ambulatoryjnego przeprowadzania leczenia – to zdecydowanie redukuje koszty terapii i zmniejsza liczbę powikłań pooperacyjnych. Innowacyjne rozwiązania skracają czas pojedynczej sesji do minimum, stwarza to komfort i wpływa na bezpieczeństwo – zarówno w przypadku pacjenta, jak i personelu. Korzyści tej metody i możliwe powikłania zostały dobrze udokumentowane w piśmiennictwie europejskim. W niniejszym artykule przedstawiono możliwości zastosowania Leksell Gamma Knife w okulistyce.

Słowa kluczowe: Gamma Knife, stereoradiochirurgia, czerniak błony naczyniowej, jaskra neowaskularna.

Stereotactic radiosurgery (SRS) is a relatively young and a very dynamic discipline. The aim of SRS is to deliver a maximum single dose of ionizing radiation to the minimum target area, while avoiding damage to the surrounding healthy tissue. The first definition of SRS was applied by the American Association of Neurological Surgeons. In 2010 it was restricted by the American College of Radiology (ACR) along with the American Society for Radiation Oncology (ASTRO) (1).

The concept of intracranial stereotactic radiosurgery was introduced by Lars Leksell in 1951. Despite several disappointing attempts, Leksell and Larson created the first model of a Gamma Knife®, and it was installed in 1968 at the Sophiahemmet Hospital in Stockholm (2). The use of crossfired radiation beams to destroy pathological tissue was simple, but it was a very innovative idea, because of the limitations of neuroimaging. Initially cisternography and ventriculography were used to identify the target (3). Submillimeter precision of the Gamma Knife radiosurgery (GKRS) required the development of high-resolution imaging technology many years later.

Therapeutic indications of Gamma Knife radiosurgery include (4, 5):

- malignant tumors of head and neck (especially metastatic brain tumors),
- benign tumors of head and neck e.g. meningioma, adenoma, schwannoma,
- arteriovenous malformations (AVM),
- trigeminal neuralgia,
- essential tremor,

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- obsessive-compulsive disorder,
- epilepsy,
- Parkinson's disease,
- ocular disorders.

Before we discuss pivotal applications of LGK in ophthalmology, it is worth getting to know how it works. Gamma-ray photons, protons, X-ray photons, helium ions, and neutrons can be used for SRS (1). They may be delivered by using linear particle accelerators (LINAC-based), gamma ray treatment devices, or by charged particles accelerators (cyclotrons) (2, 6, 7). The contemporary Gamma Knife is the only system that utilizes cobalt sources to produce gamma ray photons. Technical and practical differences between LINAC and the Gamma Knife systems are presented in Table I (2).

LGK Perfexion™ has built-in modern Gamma Plan software, which enables 3-D treatment planning and limits doses to critical structures ('risk volume' is outlined and the beams are blocked). Innovative solutions shorten a single session to a minimum, the patient is no longer moving in and out of the machine, which saves time and improves radiation protection of staff (8, 10).

The effective GKRS obviously need advanced tools. High resolution computed tomography and Gadolinium-enhanced high field magnetic resonance imaging are perfect for target localization (2, 3). In the Perfexion™ model the accuracy of the mechanical *versus* radiation isocentre is 0.05 mm (4). During implementation of imaging data (including MR imaging) the largest geometrical error and the total error in the Gamma Knife system was calculated to be 0.48 mm $\pm$ 0.23 mm (12).

	Leksell Gamma Knife/ Leksell Gamma Knife	**Leksell Gamma Knife Perfexion/ Leksell Gamma Knife Perfexion**	**LINAC-based/ bazujące na systemie LINAC**
Device/ Urządzenie	4C (previous models U, B, C)	Leksell Gamma Knife® Perfexion™	Cyber Knife, Trilogy, Novalis Tx, Synergy, Artiste, TrueBeam STx
Source of radiation/ Źródło promieniowania	Co-60	Co-60	LINAC
Target localization/ Tkanka docelowa	head and neck/ głowa i szyja	head, neck, optionally caudal cervical spine/ głowa, szyja, opcjonalnie również kręgosłup szyjny	any extracranial targeting/ dowolne umiejscowienie pozaczaszkowe
Immobilization/ Unieruchomienie	invasive frame fixed to the patient's skull/ inwazyjna rama mocowana do czaszki pacjenta	minimally-invasive frame + patient positioning system/ małoinwazyjna rama + system pozycjonowania pacjenta	frameless/ brak ramy
Fractionation/ Frakcjonowanie dawki	no/ nie	possible/ możliwe	yes/ tak

Tab. I. Technical and practical differences between LINAC and the Gamma Knife systems.
Tab. I. Techniczne i praktyczne różnice między Gamma Knife a urządzeniami bazującymi na systemie LINAC.

The Leksell Gamma Knife developed by Lars Leksell and launched by Elekta, Sweden is still in wide use. Accordingly to Elekta's statistics, approximately 60000 people are treated with LGK every year. The Gamma Knife is the most extensively studied SRS system and has the longest period of clinical use (7). Multiple Cobalt-60 sources produce gamma ray photons, which are converged and directed precisely at one point called the 'isocenter'. The single gamma ray does not harm the healthy tissue, only multiple beams crossed in the isocenter can activate an apoptosis of the lesion (8, 9). In previous models of LGK (U, B, C and still in use – 4 C) 201 cobalt sources and collimators are arranged in a hemispherical 'helmet'. In these models rigid, light stereotactic frame is fixed to the patient's skull to eliminate any movement. The frame is also essential to define coordinates of the lesion (2, 8). The most recently redesigned model, the Leksell Gamma Knife® Perfexion™, was introduced in 2006. The Perfexion unit has 192 cobalt sources. In this device a single, vast tungsten collimator is divided into eight moving sectors (each containing 24 sources in cylindrical configuration). It allows for automatic changing of the beam diameters (0, 4, 8 and 16 mm) and helps to avoid collision between the patient's frame and the inner surface of the machine (8, 10). Instead of a claustrophobic 'helmet', the newer model offers a robotized patient positioning system and a minimally-invasive frame (10, 11).

In conclusion, the advantages of the Gamma Knife are: extreme precision, single-session treatment, irradiation for multiple or eccentric targets and safe, conformal treatment planning. Minimally-invasive, fully robotized radiosurgery saves time, improves patient's comfort and decreases post-operative complications. The disadvantages are: limited accessibility, the high cost of the devices and neuroradiosurgery center, low volume of the treated lesion and its restricted localisation (head and upper cervical neck). Cobalt-60 sources also need to be replaced every 5 years, based on their half-live.

Uveal melanoma

The Gamma Knife was first used in ophtalmology by Rand et al. in 1987. He showed total regression of anterior chamber melanomas in six rabbit eyes (13). Uveal melanoma (UM) is the most common primary intraocular tumor in adults. Its incidence in Poland is estimated at 260–300 new cases per year (14). Till the late 1970 s, the enucleation of the affected eye was the treatment of choice. But Zimmerman et al. (15) proposed a revolutionary hypothesis. He suggested that surgical manipulation can cause tumor cells dissemination and may increase a risk of distant metastases. Since then many ophthalmologists have focused on non-invasive management of ocular melanoma.

Conservative treatment strategies for UM include (16–18):

- brachytherapy (most popular isotopes I 125 and Ru 106),
- transpupillary thermotherapy (TTT),
- proton beam radiotherapy (PBRT),
- helium ion irradiation,
- gamma knife stereotactic radiosurgery (GKRS),
  and very rarely: complete surgical resection, cryotherapy, laser photocoagulation, chemo- and immunotherapy.

It should be kept in mind that the ultimate goal of therapy for UM is not only to preserve a globe or useful vision, but more importantly to prolong the progression-free survival.

Over the last decade three conservative methods of treatment of uveal melanoma have been markedly developed: brachytherapy, proton therapy and stereotactic radiosurgery. It should be noted that none of these techniques is free of complications. Brachytherapy (with I 125 and Ru 106) and proton therapy gained fame as effective methods of tumor control, providing long-term survival comparable with enucleation (19–21). Suturing the radioactive plaque to the surface of the eyeball is limited by diameter and localization of the tumor – big and/ or peripapillary changes may be difficult to reach for technical reasons (16, 22–24). Moreover, brachytherapy is associated with double surgery (suturing and removing of the plaque, often with damage to the extraocular muscles), administration of high uneven doses of irradiation to the tumor surface, has an impact on the severity of ocular complications and the patient requires several days of hospitalization (23–26). Similarly to brachytherapy, proton beam irradiation is an invasive method (suturing and removing of tantalum rings) which is associated with a significant risk of complications. Despite very good long-term results, it is a laborious method that requires fractioning of the dose over a few days of hospitalization (14, 27, 28).

Stereotactic radiosurgery with the use of a Gamma Knife (GKRS) has gained many supporters in the last decade. Logani et al. (29) observed that melanoma cell lines are relatively resistant to fractioned low doses of radiation *in vitro* and the most effective was exposure to the single higher dose. GKRS was initially recommended as an alternative method of treatment for small and medium-sized UM. Its effectiveness in reducing tumor size and survival rates is comparable to brachytherapy (30), proton therapy (19, 27, 31) or enucleation (17, 32). Many authors emphasize that there is no difference between the efficacy of GKRS and enucleation, assuming death as an endpoint associated with the presence of distant metastases (17, 33). In addition to proven efficacy, an unquestionable advantage of GKRS is its minimal invasiveness. Treatment can be performed in an outpatient setting – the procedure is one-time, up to several hours and does not require surgery under general anesthesia. The only discomfort for the patient may be a need to immobilize the eye and head. Akinesia is achieved by peribulbar injection of bupivacaine or lidocaine; fixation sutures are placed under local anaesthesia to either four or two selected muscles, and threads are fixed around the patient's head (32, 34). Some authors do not use mechanical immobilization but only recommend keeping eyes closed during the entire procedure (35)! Precise imaging is crucial for radiosurgery and is achieved by using high resolution magnetic resonance imaging with intravenous gadolinium contrast (16, 26). After entering imaging data into the computer and their three-dimensional reconstruction an optimal dose of exposure is to be selected. An outlined field must ideally correspond to the size and shape of the tumor and include a margin of healthy tissue (32).

It is predictable in convex dome- and mushroom-shaped UM, but very difficult in plane and diffuse tumors – their poor demarcation may result in errors in the assessment of the involvement area, resulting in incomplete tissue destruction and tumor recurrence (34). Irradiation should achieve the intended maximum in the center of the tumor (100% isodose) and half of the size on the edge of the lesion (50% isodose) in order to minimize the risk of damage to the surrounding healthy tissue. The precise distribution of the radiation dose and minimum scattering is possible thanks to the physical phenomenon of the Bragg peak. The dose delivered in a single fraction to the tumor margin ranges in different studies from 22 Gy (36) to 90 Gy (37). It was quickly noticed that high doses of irradiation contribute to an increase of ocular complications while not improving the survival rate (38–40). Dinca et al. (17) compared a group of 170 patients with UM treated by GKRS with a dose of 35 Gy, 45 Gy and 50–70 Gy with a group of 620 people who underwent enucleation because of UM. They have not found any difference in the survival rate between the patients within the first group and between the first and the second group. Reports of other authors support the theory that the control of even large melanomas can be maintained with a marginal dose of 30-50 Gy (26, 32, 40). Schirmer et al. (36) who treated 14 patients with UM, suggested that a marginal dose less than 25 Gy provides excellent tumor control, however, despite the low dose local complications were also observed. The tumor size control (e.g., regression or lack of progression) ranges from 100% in the first half year of the follow-up (41) to 83% in the third year of follow-up (35). The eye retention rate ranges from 94% (16) to 72% (42), depending on follow-up time. The survival rates at the 3rd and 5th year were respectively 88.8% and 81.9% in Modorati et al. (32), and 94% and 86% in Sarici et al. (26). While Fakiris et al. (43) reported total survival rates of 86% and 55% after the 3rd- and 5th-year follow-up, respectively. The five-year survival rate in the report by Dinca et al. was 63% (17).

Unfortunately, the eyeball is composed of tissue highly sensitive to ionizing radiation, hence the higher the dose of radiation the greater the number of ophthalmic complications. Early transient complications after using a Gamma Knife were short-term headaches, limited subconjunctival and subcutaneous hemorrhages after mechanical stabilisation and ophthalmoscopically visible spot-like hemorrhages on the surface of the tumor (32, 34).

Late complications after GKRS described in the papers include:

- significant deterioration of vision,
- lens opacification,
- vitreous haemorrhage,
- radiation retinopathy, exudative retinopathy,
- optic neuropathy (ischemic and radiation),
- retinal detachment,
- uveitis,
- phthisis bulbi,
- uncontrolled neovascular glaucoma (NVG).

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Observation time is critical to note complications. It seems that follow-up of less than 6 months is not long enough for all the complications to manifest. More than 90% of them can only be observed 24–48 months after the treatment cessation (32).

Tumor size and location also play an important role in prognosis. Large tumors located in anterior and intermediate uvea were related to higher incidence of the most serious complication – painful neovascular glaucoma (26, 34). In the cited literature NVG, in addition to the UM recurrence, is the most common post-treatment cause of enucleation – this concerns not only GKRS but also other methods of radiotherapy (17, 24, 44, 45). Egan et al. (46) and Langman et al. (34) emphasize that a cilliary body melanoma of over 8 mm in height and/ or 10 mm in largest basal diameter is related to a higher risk of neovascular glaucoma development and subsequent enucleation. Is seems that an accurate tumor evaluation and exposure dose reduction decreases the GKRS incidence of side effects (17, 34–36, 43). Treatment of proximally located tumors is also related to cataract development, which is the only complication to be successfully operated on. GKRS for posterior eye segment, particularly for the macular and optic disc area, increases the risk of radiation retinopathy and neuropathy occurrence. Schirmer et al. (36) emphasizes that regardless of the dose in each treated patient maculopathy develops, if a tumor in the macular area is submitted to treatment. According to Stafford et al. (47) the risk of optic neuropathy after GKRS to the head is scarce (it amounted to 1.9% in a group of 215 people), and directly proportional to the radiation dose absorbed by the optic nerve. The results are contrary to the observation of Zehetmayer et al. (45), who reports optic neuropathy in 26% of patients, after a single dose of 45–50 Gy in UM treatment.

A significant reduction of visual acuity was present in almost all patients treated with a Gamma Knife, regardless of the size of the treatment group. Sarici et al. (26) noticed in 60% of patients after GKRS visual acuity at the level of 20/200 or worse, while at the moment of UM diagnosis median BCVA was 20/60. Modorati et al. (32) reports a reduction of visual acuity by 94% at the end of the follow-up, while Mueller et al. (16) describes in a one-year follow-up BCVA decrease from 20/60 to 20/200. Dinca et al. (17) points towards dependence of vision deterioration on the applied treatment dose – BCVA decrease after treatment was significantly lower in the 35 Gy group than in the 45 Gy group (31.4% vs. 83.7%). In order to minimize the risk of complications, all authors recommend reasonable qualification of patients for treatment with a Gamma Knife. It is necessary to analyse the key parameters: tumor size, its location and choice of proper radiation dose.

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