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Various aspects of radiosurgery – a review

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Abstract

Introduction and purpose

Radiosurgery (RS) is an innovative treatment method that involves the precise administration of a large dose of ionizing radiation to the diseased area of the body sparing healthy tissues maximally. The treatment is non-invasive and usually painless for the patient, and its greatest advantage is the immediate destruction of cancer cells. The method enables the treatment of tumors which are located within the brain tissue, but also of extracranial lesions in almost all organs of the human body. The aim of this article is to compare the structure, principles of operation, advantages, disadvantages and the use of Gamma Knife and CyberKnife in neurosurgery. These devices are used to perform radiosurgery and stereotactic radiotherapy procedures. They are an alternative to neurosurgical procedures, especially for cancerous tumors located in hard-to-reach places, and significantly reduce the risk of postoperative complications.

Materials and methods

The literature included in the PubMed, BioMed Central and Polish Medical Platform databases is searched by means of the words such as Gamma Knife, CyberKnife, radiosurgery, stereotactic radiotherapy. Quoted sources in selected works were also used.

Conclusions

Stereotactic radiosurgery is an element of radical, palliative or analgesic treatment of well-circumscribed small lesions, less than 5 cm in diameter. Gamma Knife and CyberKnife enable cancerous and non-cancerous treatment lesions. Both procedures are performed on an outpatient basis and are considered minimally invasive procedures, especially recommended for patients who cannot undergo neurosurgical surgery or require less invasive cancer treatment. Gamma Knife was designed for radiosurgery of lesions located intracranially and covering the upper parts of the cervical spine up to the level of the fourth cervical vertebra, while CyberKnife or modern linear accelerators are used for intracranial and extracranial radiosurgery.

Key words:

gamma knife, cybernetic knife, radiosurgery, stereotactic radiotherapy

Introduction

In the 1950s, Swedish neurosurgeon Lars Leksell, in cooperation with Borje Larsson at the Karolinska Institute in Stockholm, began working on the development of the technique of stereotactic radiosurgery [1]. In 1968, they introduced the first Gamma Knife device into clinical practice, which directs gamma radiation 192 sources of cobalt 60 beams into the diseased area of the brain. Single beams of rays have low energy and do not damage the surrounding tissues. The collimator (diameter 4 mm, 8 mm, 14 mm and 18 mm) precisely directs the beams at the pathological lesion, their energy adds up and causes necrosis of cancer cells [2,3]. Gamma Knife was designed for the treatment of functional disorders (tremor in Parkinson's disease), but with technical progress its clinical usefulness increased and it was widely used in other intracranial lesions treatment (primary, recurrent tumors, brain metastases) [3-5]. After 50 years of development of this technology, it is estimated that approximately 1 million patients all over the world have received the therapy [6]. CyberKnife was invented in Stanford Health Care by American neurosurgeon John Alder and debuted in 1994 [7]. The device is one of the linear accelerators that has the highest precision and the shortest treatment duration. CyberKnife combines a compact linear accelerator placed on a robotic manipulator and an integrated image guidance system that records stereoscopic images and controls the manipulator to position precisely the therapeutic beam into the area that is affected by the cancer [8,9]. The accelerator is also equipped with a tracking system that allows you to track a moving target in real time. The structure of the device allows for irradiation of lesions located anywhere in the patient's body, movable tumors (liver, lungs) or immobile tumors with very high precision, which reduces the risk of toxicity to adjacent healthy tissues [10, 11].

Objective of the work

The aim of this study is to compare the structure, working principles, advantages, disadvantages and application of Gamma Knife and CyberKnife in neurosurgery.

Description of the state of knowledge

The widespread use of radiotherapy and stereotactic radiosurgery is possible thanks to the development of CT, MR and PET imaging techniques as well as computer technology and software. PET is used to assess the extent and anaplasia degree and also prognosis which is based on the metabolic activity of the tumor [5, 12]. It is possible to develop a detailed treatment plan unique to each patient when you support this research. Then the plan is approved by a neurosurgeon, radiotherapist, radiologist and medical physicist [1, 13].

Gamma Knife

The first Gamma Knife models that revolutionized classic neurosurgical treatment methods were: model U, model B and model C [14]. In the U model, the bed on which the patient was lying was lifted up after being placed in the device by means of a hydraulic drive. In order to improve safety, the hydraulic system in model B was replaced with an electric motor [15]. Another difference between the models was the way the patient was positioned. In model U, the patient took a prone position, while in model B this was not required. In order to hasten the procedure and avoid errors in manual determination of stereotaxic coordinates, the C model has been used for treatment since 1999 [15, 16]. The most important advantage of this device is the Automatic Positioning System (APS), which enables automatic change of the patient's position before the next dose of radiation [17]. APS guarantees greater precision by increasing the number of individual doses with lower energy. It also provides the delivery of lower doses of radiation to areas that are not affected by pathology [18, 19]. The ease of use of the helmet with color-coded collimators and occlusion plugs are other advantages of the C Gamma Knife model [20].

In the models presented above, ionizing radiation is directed through a semicircular helmet that is attached to the table on which the patient lies. Replacing helmets is a time-consuming process, so it was decided to develop a technique that would speed the procedure up and would not require changing helmets during the procedure. In 2006, the Swedish company Elekta introduced the Gamma Knife Perfexion, which did not have such helmet. (Fig. 1) [2, 3, 10, 19].

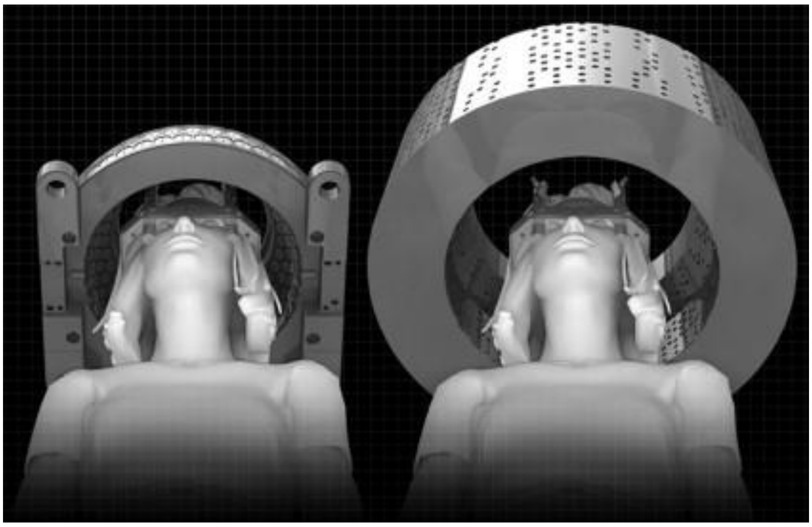

Fig. 1 Difference in the construction of the Gamma Knife.
On the left, a model of the previous Gamma Knife, on the right, Gamma Knife Perfexion
Source: Jeremy C. Ganz, Chapter 13 - Changing the gamma knife, Elsevier, Volume 215, 2014

Leksell Gamma Knife Perfexion

Due to the increasing use of Gamma Knife in the treatment of metastatic lesions in the brain, it was necessary to introduce modifications to the current method of treatment. The metastases were located in different places, they were multiple and had different sizes, therefore the holes in models with helmets were insufficient and prevented access to all lesions [21]. Automating collimators exchange in the device allows you to reach each tumor and shorten the procedure time because manual replacement of helmets is not necessary [22].

Leksell Gamma Knife Perfexion is not a modification of the existing Gamma Knife models. It is a modern device whose method of operation does not differ from the previous ones. The radiation comes from 192 cobalt 60 sources (cobalt energy - 1.25 MeV, half-life - 5.25 years) and it is formed by collimators with a selected diameter (4, 8, 16 mm). The size of the collimator determines the size of the gamma radiation beam that is focused on the designated area of the lesion. Thanks to the use of collimators, the treatment is very detailed, with an accuracy of 0.15 mm. The other elements of the device are: a control console, a therapeutic table located in the isocenter, to which a stereotaxic frame is attached (Fig. 2) [14, 23, 24].

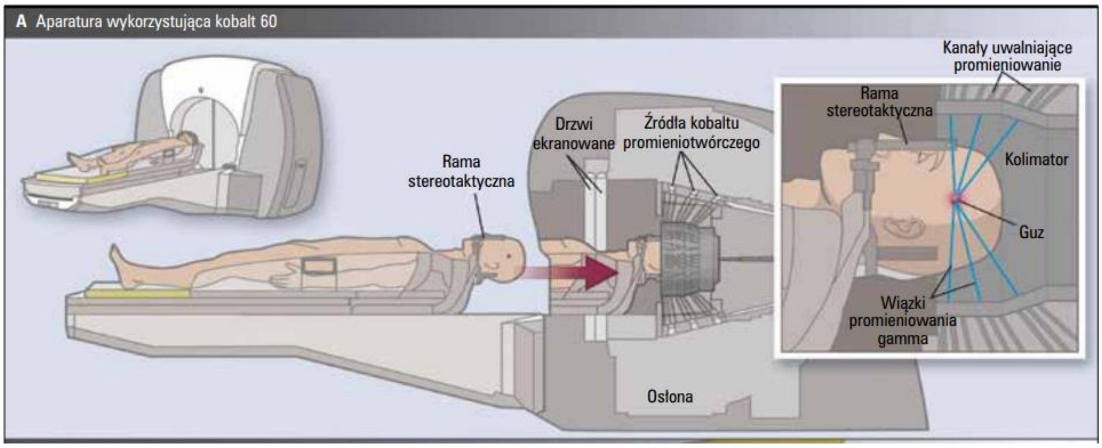

Fig. 2 Stereotactic radiosurgery using Gamma Knife
Source: Stereotactic radiotherapy in the treatment of patients with brain metastases, Oncology after graduation (2011) Vol.8 (11), 11

After prior qualification (interview, patient examination, neuroimaging tests) by a neurosurgeon, the patient can be prepared for the procedure. The doctor discusses with the patient the purpose and method of treatment and presents possible side effects, which include: brain edema, radiation necrosis, and seizures. development of neurological deficits or the appearance of new ones.

The treatment procedure consists of several stages:

1. Installation of a stereotaxic frame by a neurosurgeon. The frame is placed under local anesthesia with four titanium screws that are inserted through the skin into the skull bones. Then it is rigidly attached to the table the patient is lying on, which ensures high irradiation accuracy.
2. Performing neuroimaging. A CT examination with an appropriate selection of parameters or an MRI of the head is most often performed in appropriate sequences (T1, T2 imaging, layer thickness approx. 1 mm, 3D, examination with or without contrast). In some cases, angiographic examination of cerebral vessels is necessary. This allows you to determine stereotaxic coordinates and establish a treatment plan.
3. Developing a treatment plan involves determining the appropriate dose of radiation and targeting the area of pathological change, while minimizing the dose in the area of normal nervous tissue. Unwanted irradiation of physiological brain structures may lead to neurological complications.
   First, you need to define the skull (head measurements, CT) and the matrix. The matrix is a cubic computational grid that has 31 computational points in each direction, and its size affects the accuracy of the calculations (the smaller the matrix is, the more accurate the calculations are). When determining the matrix, the therapeutic isodose, i.e. the line connecting points with the same radiation dose, should also be taken into account. The radiation dose is determined based on the size, shape, type and location of the lesion. (Table 1).

Table 1 Examples of therapeutic dose values used in Gamma Knife

Type of change	**Therapeutic dose**
meningioma	12-16 Gy in 50% isodose
neuroma	12 Gy in 50% isodose
brain metastases	16-24 Gy in 50-80% isodose
hamartoma	12-20 Gy in 50% isodose
paraganglioma	16-20 Gy in 50% isodose
neuralgia	85-90 Gy in 100% isodose
Parkinson's disease	130 Gy in 100% isodose

Source: A. Mitek, K. Antończyk Szewczyk, How to properly plan therapy with the Gamma Knife device. Engineer and Medical Physicist, (2018), Vol. 7(4), 273 276

4. Once the plan is created, it is approved by the neurosurgeon, radiotherapist and medical physicist. The following parameters are assessed: gradient index, coverage,

selectivity, maximum doses (90% isodose) and doses to critical organs, e.g. the brain stem, which cannot exceed 15 Gy.

5. Verifying calculated doses in Gamma Plan Mu-Check, which recalculates doses at specific points. Doses at the point for isodose 95%, 90%, 80% and 50% are checked. The difference between the calculated dose in the system and the planned dose cannot exceed 5%.
6. Placing the patient in the Gamma Knife. The patient should be immobilized on the therapeutic table by means of a stereotaxic frame and then the radiation module should be started. Radiation usually lasts from several to several dozen minutes, and the patient is fully monitored throughout the session.
7. After completing the procedure, the patient leaves the hospital within two hours, as painkillers are often required after removal of the stereotactic frame [13, 25-27].

Leksell Gamma Knife Icon

Gamma Knife Icon is the most precise device used in stereotactic radiosurgery on the market. The device has a number of innovations such as: integrated imaging and computer software that analyzes the administered dose in order to control the radiation beam constantly in relation to the position of the patient's head. This allows you to easily eliminate errors related to irradiation of areas not affected by the pathological process due to the change in the patient's position. Previous Gamma Knife devices offered single-fraction treatment using a stereotaxic frame that was placed under local anesthesia, and often resulted in headaches and pain where the screws were placed. Gamma Knife Icon uses both frame and frameless treatment (Fig. 3) enabling multiple fractional radiation or hypofractionated technique [28].

Fig. 3 Stereotactic radiosurgery using Gamma Knife Icon. The device does not have a stereotaxic frame attached to the table. Source:Desai R, Rich KM. Therapeutic Role of Gamma Knife Stereotactic Radiosurgery in Neuro-Oncology. Mo Med. 2020 Jan-Feb;117(1):33-38.

Advantages and disadvantages of Gamma Knife treatment

Advantages:

- Non-invasive
- Submillimeter precision and beam stability
- Minimal doses directed to healthy body tissues
- No need for hospitalization
- No risks associated with craniotomy and neurosurgery
- Quick return to daily activities, usually after 24-48 hours, maximum after seven days

Disadventages:

- Need to replace sources every 6-7 years
- Placement of the frame under local anesthesia and possible pain after removal
- The size of the lesion treated does not exceed a diameter of 4 cm
- Treatment of lesions affecting the brain and upper cervical spine, cannot be used in extracranial locations
- No treatment possible for infants (immobilization in a stereotaxic frame is impossible due to the presence of fontanelles) [29, 30]

CyberKnife

CyberKnife is a linear accelerator that emits radiation beams with a maximum energy of 6 MV with millimeter or submillimeter accuracy of 0.05 mm. Doses are administered non-isocentrically, which provides uniform distribution [31]. The device is equipped with a constant monitoring system that allows you to track the patient's movements in real time, thanks to it the accelerator re-aligns the beam depending on fluctuations in the position of the pathological area caused by the patient's movement. The device is used in stereotactic radiosurgery (SRS), hypofractionated stereotactic whole body radiotherapy (SBRT), selective 3D conformal radiotherapy (3D-CRT), and intensity-modulated radiotherapy (IMRT) [32,33]. It enables the treatment of respiratory-mobile tumors (liver, prostate, lung) or immobile tumors while sparing healthy tissue surrounding the lesion. The dose outside the target area is 2-6 times higher than with Gamma Knife [34-37]. Unlike other methods of radiosurgery and stereotactic radiotherapy, CyberKnife does not use invasive methods of immobilization, thus minimizing the possibility of side effects [12, 33]. The linear accelerator is located on the robot's arm, which allows radiation to be emitted from up to 1,600 positions, allowing for a homologous dose distribution and free movement of the device around the patient (Fig. 4). According to a 2003 study conducted at Stanford University, the radiation accuracy was determined to be 1.1±0.3 mm when CT section thicknesses of 1.25 mm were used. [37, 38, 39].

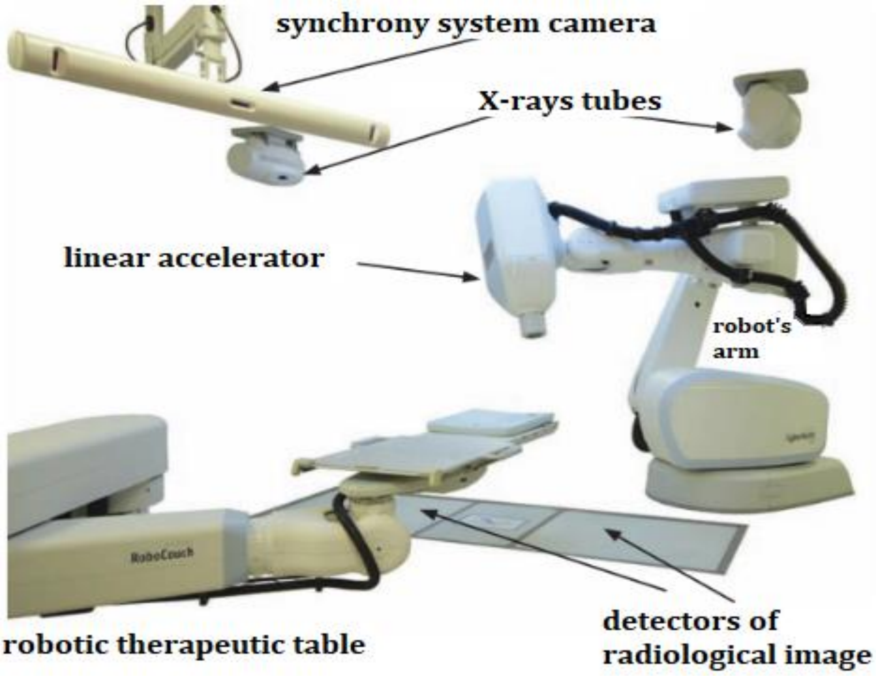

Fig. 4 CyberKnife device with 6 degrees of freedom, therapeutic table, Synchrony system camera, X-ray tubes
Source: Department of Radiotherapy, Oncology Center Institute. Maria Skłodowska-Curie Branch in Gliwice, Information (2014)

The treatment procedure consists of the following stages:

1. Qualifying a patient for the procedure involves collecting an interview, physical examination of the patient and ordering imaging tests: CT, MRI, PET, biochemical and molecular tests by a radiotherapist.
2. Marking (optional) involves implanting gold markers in the place of the treated lesion. The procedure is usually performed on the same day as the radiation procedure or requires one-day hospitalization due to the need for anesthesia. The markers are reference points that allow you to track the tumor and precisely locate the lesion. The doctor decides to place the markers after analyzing the imaging tests.
3. Performing neuroimaging. Most often, a CT, MRI or PET scan is performed in order to locate precisely the area affected by pathology and normal tissues within the lesion. The AutoSegmentation function enables accurate and automatic delineation of critical structures.

4. Development of a treatment plan by a multidisciplinary team, including a radiotherapist, a neurosurgeon and a medical physicist. The doctor determines the area that should be irradiated by means of the radiation dose and identifies critical structures. Then the medical physicist prepares the most optimal treatment plan. QuickPlan automates several aspects of the planning process, making it easier to achieve the most complex planning goals, but also predicts and optimizes treatment times based on individual patient needs.
5. Construction of a stabilizer, which consists of preparing a vacuum mattress and a mask to immobilize and stabilize the patient's position during therapy.
6. During the procedure, the patient is immobilized on the therapeutic table using a stabilizer. The patient's position is constantly monitored by an X-ray tube. Synchrony Respiratory Tracking leverages the robot's mobility to dynamic delivery of each radiation beam, automatically adapting to changes in the patient's breathing pattern during each treatment fraction.
7. CyberKnife radiotherapy is an outpatient procedure. Patients can quickly return to daily activities, a few days after radiation.
8. During and after treatment, the tumor is inspected, its regression is assessed and any metastatic tumors in another part of the patient's body are identified [40, 41].

CyberKnife radiotherapy usually lasts from 45 minutes to 2 hours and is performed on days 1-5 sessions.

Advantages and disadvantages of CyberKnife treatment

Advantages:

- Non-invasive method
- No anesthesia was used
- No risk associated with surgery and no post-operative complications
- Reducing the intensity of post-radiation complications
- Possibility of using therapy at an early stage of cancer
- Possibility of treatment throughout the body, intracranially and extracranially
- Possibility of correction due to patient movement or displacement of the lesion

Disadvantages:

- Difficulties in treating patients who have restless movements and cannot maintain a stable position, e.g. elderly patients with bladder instability
- The need for sedation in the treatment of children for immobilization
- Necessity to place markers [35, 37, 38-40]

Selected disease entities

Metastatic tumors to the brain

The cancers that metastasize to the brain most often according to the order of frequency are: lung cancer, breast cancer, melanoma, gastrointestinal cancer, and kidney cancer.

In studies from 2014 and 2015 the amount of radiation dose applied depending on the type of radiosurgery is compared to the method chosen - Gamma Knife or CyberKnife. Y.H. Cho and colleagues studied 77 patients with large (>3 cm) brain metastases (n=40) and small (<3 cm). 88 lesions were exposed to an average radiation dose of 22 Gy using the Gamma Knife, and 38 large lesions were delivered 3-4 fractions of radiation from the CyberKnife device with an average value of 35 Gy. After analyzing the results, the researchers concluded that fractionated doses of X-ray radiation by means of CyberKnife were comparable to single doses of Gamma Knife in the treatment of small metastases, suggesting the validity of using both methods for the treatment of these lesions [42, 43].

Due to the development of the Gamma Knife Icon, which does not have a stereotaxic frame, H. Y. Park conducted a study on the effectiveness of treating large brain metastases using this device. The study was conducted on 15 patients with 17 lesions larger than 10 cm^3. The tumor volume decreased in 13 cases and remained unchanged in 4 cases. New changes were observed in one patient and one death was reported. The results of this study turned out to be good and promising, so a large cohort study is planned to clinically confirm the effectiveness of the new Gamma Knife model in this disease [28, 44].

Trigeminal neuralgia

The main symptom of trigeminal neuralgia are attacks of pain in the area of half of the face within the innervation of the V nerve. At the beginning, the pain is sudden and its duration ranges from a few seconds to 2 minutes. It may be limited to one or all three branches of the V nerve. Stereotactic radiosurgery is the second non-invasive treatment method after pharmacotherapy [13]. A study conducted by Latoreff and his colleagues on 1,943 patients who underwent stereotactic radiosurgery from 2008 to 2011 shows that a beneficial therapeutic effect was achieved in approximately 60% of those treated in this way. However, it should be emphasized that the most effective method of treating trigeminal neuralgia remains microsurgical decompression [45, 46].

Conclusion

Stereotactic radiosurgery which involves administering a single dose of radiation using the Gamma Knife technique and usually administered in several sessions using the CyberKnife method and gamma radiation, gives good results and relatively fewer complications than conventional neurosurgical treatment. The basic indications for the use of the above-mentioned techniques are changes located internally - only in the case of Gamma Knife, internally and extracranially - in the case of CyberKnife. It is worth noting that the best results of radiotherapy are achieved with tumors smaller than 3 cm (Table 2).

Tab. 2 Comparison of some features of Gamma Knife and CyberKnife [47]

Gamma Knife	**CyberKnife**
Gamma radiation emission (source: radioactive cobalt)	Emission of photon radiation
Isocentric radiation dose distribution	Homogeneous radiation dose distribution
Treatment of lesions in the brain and upper cervical spine C4	Treatment of lesions throughout the body, irradiation of respiratory-mobile tumors
Accuracy approx. 0.15 mm	Accuracy approx. 0.05 mm
Head immobilization using a stereotaxic frame	No need for invasive patient immobilization
The treatment is performed during one session	Single or multiple treatments

DISCLOSURE

Author's contribution:

Conceptualization, supervision and project administration: Marta Kozikowska, Bożena Kmak, Anna Szot,

Methodology: Marta Kozikowska, Bożena Kmak, Anna Szot

Software, validation, formal analysis, investigation, resources, writing original draft preparation: Bożena Kmak, Marta Kozikowska, Anna Szot

Writing review editing and visualization: Anna Szot, Bożena Kmak, Marta Kozikowska

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