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Information for doctors and patients considering the application of CyberKnife® radiosurgery for

Glioma - Astrocytoma, Glioblastoma Multiforme, Oligodendroglioma

IMPORTANT NOTE

The following is drawn from information provided by Accuray Inc., USA, the manufacturers of CyberKnife® and providers of a range of supporting medical software and is offered for general guidance. Medilux Healthcare Ltd. takes no responsibility of the accuracy or otherwise of statements contained herein. To check for the most recent guidance on treatment protocols for any particular conditions visit www accuray.com

CyberKnife® treats a range of cancers and other medical conditions and there are now many CyberKnife® centres around the world, but not all countries yet have one and some centres specialise more in certain areas than in others or only accept international patients for specific types of treatment. CyberKnife® is a remarkably effective tool for certain cancers and medical conditions but cannot be used for others.

Based on our practical experience in handling a great many enquiries for the European CyberKnife® Centre in Munich, Germany, Medilux Healthcare Ltd. provides information to doctors and patients worldwide as to the range of conditions treated, the parameters which generally apply to assessment of cases and how to apply for treatment. We continue our close co-operation with Munich but we now also handle new patient and doctor enquiries for a growing number of CyberKnife® centres worldwide.

What is a glioma?

Gliomas are a class of tumour that develops from glial (neuroepithelial or support) cells. Astrocytes, ependymal, and oligodendroglial cells are all examples of glial cells that compose the supportive tissue of the brain. Gliomas comprise nearly one-half of primary brain tumours and one-fifth of all primary spinal cord tumours. Contemporary classification of gliomas is based on the World Health Organization (WHO) system, which classifies the tumours according to the cell of origin and histologic features identified by the pathologist or neuropathologist.

Low grade gliomas are slow growing, and are assigned either a I or II grade. From a practical standpoint, grade I tumours (such as the pilocytic astrocytoma) are usually excluded from conversation dealing with gliomas, as they constitute a distinctive pathologic and clinical entity. High grade (malignant) gliomas grow much more quickly, and are assigned either a III (anaplastic) or IV (glioblastoma multiforme) grade. Combined, grade III and IV gliomas represent about 40% of all primary brain tumours in patients aged 40-49 years, and 60% in patients older than 60 years. In most clinical series, grade III tumours comprise approximately 10% and grade IV 90% of the total number of high grade, malignant primary brain tumours.

Malignant gliomas are one of the most devastating tumours that can affect any given individual. Nevertheless, this past decade, major advances in the fields of molecular biology and cellular biology, as well as genomics, has begun to improve our current understanding of malignant gliomas. Grade IV gliomas, often referred to as Glioblastoma Multiforme or "GBM", possess multiple genetic and chromosomal abnormalities which cause these tumours to grow rapidly. These tumours are unique in their capacity to proliferate uncontrollably and aggressively invade, infiltrate and destroy neighbouring areas of the brain. However, it is very rare for such tumours to metastasise (spread) outside the central nervous system.

As a GBM progresses, portions of the tumour often outgrow the immediate blood supply and die or "undergo necrosis". In contrast, peripheral regions of the tumour readily recruit the growth of new blood vessels (angiogenesis), enabling continued rapid growth of the GBM. The aforementioned features of grade IV gliomas occur simultaneously within a given tumour cell population, resulting in a heterogeneous histologic and genetic mosaic pattern, hence, the term Glioblastoma Multiforme.

What are the signs and symptoms of a glioma?

The presenting symptom(s) of a glioma depend on the location of the tumour within the brain and its rate of growth. Common symptoms include: headaches, seizures, difficulty speaking, weakness/paralysis in one part of the body or face, difficulty with vision, impairment of sensation, impairment of balance, nausea/vomiting, behavioural changes, and impairment of memory or thinking. The clinical course of an untreated malignant glioma is characterized by relentless invasive growth and, even with treatment, near universal recurrence.

How is a glioma diagnosed?

The majority of patients harbouring a malignant glioma have had one or more of the aforementioned clinical symptoms of varying duration (usually weeks to months). Occasionally, a patient may present with no prior neurological symptoms. In this uncommon scenario, the glioma is discovered “incidentally” on a head CT scan performed on a patient for other reasons, such as an auto accident or a fall with associated head trauma.

In evaluating most brain tumours, magnetic resonance imaging (MRI) of the brain is usually preferred over a CT scan. MRI is better at establishing a presumptive diagnosis and delineating the suspected brain tumour in three planes, thereby allowing more exact localization of the tumour in relation to critical areas of the brain. Multi-voxel magnetic resonance spectroscopy (MRS) is now readily available at most medical centres. MRS is capable of characterizing the “chemical fingerprint” of a brain lesion non-invasively. Furthermore, positron emission tomography (PET) scanning can provide information about the metabolic potential of a brain lesion; a more intense signal suggests a greater reproductive potential, and in the case of a glioma, a more aggressive and faster-growing tumour.

Although these non-invasive diagnostic tests are helpful, the gold standard for accurate diagnosis of a glioma is a pathologic examination of tissue samples obtained from biopsy. The field of neuropathology is quickly being redefined by the use of highly specific immunologic and molecular markers. Such tests use special (histologic) stains that are linked to an antibody that specifically binds to a particular receptor on the surface of either normal cells or tumour cells. The receptors on the surface of the cell are controlled by a special code designated by a particular gene in the cell’s nucleus. An aberration in the gene controlling the blueprint of the cell’s surface receptor will produce a corresponding aberrancy on the surface receptor of the cell. The complex structure consisting of the special stain, the antibody and the cell surface receptor on the tumour cell form a so-called “tumour marker”. These markers can now be identified and characterized, facilitating the diagnosis of a malignant glioma, and eliminating the guesswork of traditional methods. Once a definitive diagnosis has been established, a customized treatment plan is developed for the individual patient, based on his or her unique circumstances.

What treatment options are available for malignant glioma?

Traditional treatment options for malignant gliomas include: surgery, radiation therapy and chemotherapy.

Surgery

Open surgery, through a window cut into the skull (craniotomy), is the primary form of treatment for malignant gliomas. The goal of surgery is to remove as much of the visible tumour as possible without damaging normal neurological functions. The invasive and infiltrating nature of malignant gliomas make this a very challenging task, despite recent advances in operative neurosurgery. Fortunately, an array of new technologies, such as operating microscopes, microdissection techniques, intraoperative computerized image-guidance, intraoperative ultrasound, intraoperative brain mapping, and most recently, real time MR imaging, makes surgical resection of gliomas safer than ever. Among patients with anaplastic astrocytoma and glioblastoma, there appears to be a definite increase in survival in those patients who have had at least a 97% or greater resection of their tumour, and in those patients whose tumour is located in the frontal lobe of the brain, as opposed to the temporal or parietal lobes.

Although not curative, aggressive removal of malignant glioma can immediately alleviate symptoms caused by the mass of a tumour and improve the effectiveness of other therapies; if not removed, the hypoxic/necrotic central portions of a tumour tend to be particularly resistant to radiation and chemotherapy. Furthermore, resection of a malignant glioma provides the neuropathologist with the best possible tissue sampling and permits an optimal histologic and genetic analysis of the tumour.

Radiation therapy and chemotherapy

Radiation therapy and chemotherapy are widely used as secondary or adjuvant treatments following surgery. Both therapies have a growth-suppressant effect on the tumour. Among patients who are not surgical candidates, either radiation or chemotherapy can be used as an initial treatment, but typically only after a biopsy has established the diagnosis of malignant glioma. Patients who are poor operative candidates generally include those who:

1. are medically unstable
2. have multiple active cancers simultaneously
3. have tumour spread to both brain hemispheres
4. have a glioma in an inoperable location (e.g. brain stem)
5. are opposed to surgery

A therapeutic role for postoperative radiation therapy was clearly established 25 years ago in a randomised trial carried out by the Brain Tumour Cooperative Group. In this study, the 14-week mean survival for patients undergoing surgery alone was extended to 42 weeks by the administration of daily (fractionated) radiation therapy delivered over a 6-week period of time. The typical total dose of conventional radiation therapy used to treat malignant gliomas is approximately 60 Gray (Gy). Such treatment is delivered to the tumour, plus a 2-3 cm margin surrounding the tumour, as determined on either a preoperative MRI or CT scan. The purpose of the additional margin of radiation is to compensate for less than perfect beam alignment and to treat the area of surrounding normal brain that is in the process of being infiltrated with tumour cells that are not visible by either MR or CT imaging.

With conventional radiation therapy, the daily dose is intentionally kept low and the technique of delivery is designed to maintain a uniform intensity of radiation, i.e. dose homogeneity. This latter concept ensures that no area of the tumour or surrounding normal brain receives too large or small a dose of radiation. Unfortunately, substantial regions of normal-functioning brain can be injured by the significant margin included in the radiation field.

Typical modern radiation therapy uses a linear accelerator to fire beams of radiation at a tumour from several directions. Most contemporary methods of radiation therapy use computer-controlled beam shaping devices to better conform the target volume to the shape of the tumour being treated. The best of these techniques, termed Intensity Modulated Radiation Therapy (IMRT), uses a computer to vary the intensity and shape of each radiation beam. The net benefit of IMRT is to better conform the dose of radiation to the tumour, even when the lesion has a very complex shape.

Complications of Radiation Therapy

With conventional daily-fractionated radiation therapy, the common short-term side-effects (which occur in days to weeks) are fatigue, loss of appetite and nausea. Skin rashes and hair loss often also occur over substantial regions of scalp. Delayed side-effects (occurring within months to years) can include varying degrees of memory loss and impairment of reasoning or thinking. More rarely, patients can experience impairment of pituitary function or radiation necrosis (a collection of dead tumour cells and scar tissue). Radiation necrosis can produce symptoms that are often very similar to the initial tumour presentation and includes severe headache, motor weakness, visual problems, or seizures.

What is the role of stereotactic radiosurgery in the treatment of gliomas?

Inevitably, high grade glial tumours will recur (progress) despite aggressive surgical removal and even the best of radiation therapy. Recurrence will usually develop at the margins of previously resected and irradiated tumour in approximately 80% of the cases. To delay tumour recurrence, a large, single dose of radiation (radiosurgery) is sometimes used to "boost" the original location or "tumour bed", with a particularly intense dose of radiation. Such radiosurgery is administered to a sharply delineated region of the tumour bed after resection and standard irradiation. Unlike conventional radiation therapy, which seeks simply to suppress the growth of the glioma, the goal of radiosurgery is to create a zone of tumour destruction. In addition, radiosurgery can be used to ablate glial tumours in patients who are otherwise not surgical candidates, patients who cannot tolerate daily radiation, and patients who are opposed to conventional surgical resection. Whether used immediately following surgery, or at the time of glial tumour recurrence, clinical studies suggest that radiosurgery prolongs patient survival.

Although there are several types of devices used to administer radiosurgery, the principle of delivering a high dose of radiation to a precisely localized target is the same. Some technologies, like the Gamma Knife, use radioactive cobalt as a source of ionizing radiation. A linear accelerator produces the radiation in other devices. Regardless of the source of radiation, nearly all methods of radiosurgery use stereotactic frames that are anchored to the patient's skull with invasive aluminium or titanium screws. The frame serves to accurately localize the tumour in space and immobilize the patient's head. The CyberKnife[®] is the only radiosurgery device that does not require such a frame for precise targeting. As a result, this instrument uniquely enables doctors treating gliomas to divide a large radiosurgical dose into more than one stage or fraction staged radiosurgery. Staged CyberKnife[®] radiosurgery is of particular benefit to patients who have previously received large doses of conventional radiation therapy and patients with gliomas located near critical areas of the brain.

What are the advantages of CyberKnife[®] radiosurgery for gliomas?

In addition to offering the benefits of staged treatment, CyberKnife[®] radiosurgery also eliminates the pain and discomfort associated with attachment of the head frame used with other radiosurgery devices. With the CyberKnife[®], there are no incisions or puncture sites from screw placement, no potential for bleeding or infection, no pain, and no post-procedure recovery time. Furthermore, the unique robotic non-isocentric targeting system of the CyberKnife[®] makes it possible to better conform a dose of radiation to the often irregular shape of malignant gliomas.

What can I expect following CyberKnife[®] radiosurgery?

Following CyberKnife[®] radiosurgery treatment, patients return home. Infrequently, some patients may experience transient dizziness, light headedness, or mild headaches that are amenable to a short course of corticosteroid medication. Patients who have been on anti-seizure medications will remain on these until advised otherwise by their primary neurologist/epileptologist or neurosurgeon. Although most glioma patients are given medicines (steroids and anti-convulsants) immediately after radiosurgery to prevent seizures, post-radiosurgery seizure events remain a rare but potential complication of radiosurgery. Hair loss after any radiosurgery is possible, but quite unusual, and when it occurs, is usually limited to small portions of scalp. Longer-term use of radiosurgery, including the CyberKnife[®], is also associated with a small but definite risk of radiation necrosis. When such a problem arises, symptoms can usually be managed with steroid medications and anticoagulation for selected patients.

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What are the differences between the common radiosurgery technologies?

Several SRS systems are available for the treatment of patients. The most widely used SRS devices include: cobalt-sourced systems (Gamma Knife), modified linear accelerators, and the CyberKnife®. All of these devices, if properly operated, are capable of delivering the desired radiation dose to a designated target. However, for certain clinical situations, there can be important differences between these devices, which for some patients may have a significant impact on clinical outcome. CyberKnife® System

CyberKnife® System

The CyberKnife® System is an SRS system utilizing contemporary technology that is designed to be the most accurate and flexible tool available for aggressive therapeutic irradiation. The CyberKnife® was designed to address the limitations of frame-based SRS systems and expands the application of radiosurgery to sites outside of the head. It is the only system to incorporate a miniature linear accelerator mounted on a flexible, robotic arm. An image-guidance system that can track target location during treatment also enables the CyberKnife® to offer superior targeting accuracy without the need for the invasive head frame. While Gamma Knife and linac-based systems can perform radiosurgery in the brain, true radiosurgery for areas outside of the brain is difficult if not impossible to perform with these systems.

Advantages of the CyberKnife® include:

- No invasive head frame or other rigid immobilization device is required
- The ability to perform radiosurgery (1-5 fractions) on targets throughout the body, not just the brain and spine
- Precise targeting (within 1 mm) of selected lesions in the brain and body
- A unique ability to provide real time monitoring of the treated target throughout treatment using an advanced image-guidance system
- A unique ability to correct during treatment for limited target motion (e.g. due to small patient movements) - - The capacity to easily perform staged radiosurgery
- Because the CyberKnife® system is so accurate as well as versatile and painless, it is often the radiosurgical procedure of choice from a patient's perspective.

Disadvantages of the CyberKnife® include:

- The need for placement of very small markers (fiducials) via a needle for the treatment of targets outside of the head

[Note: by using additional medical software the European CyberKnife® Centre is also able to treat targets in the spine without fiducials]

- Compared to other radiosurgical devices, treatment takes longer when multiple tumours are ablated during the same treatment session.

Cobalt-Sourced Systems (Gamma Knife)

The first radiosurgical device was conceived and developed in the 1950s by Professor Lars Leksell at the Karolinska Institute in Stockholm, Sweden. His work culminated in the development of the Gamma Knife (Elekta Inc), which was used to treat patients beginning in 1968. This device is capable of precisely irradiating small intracranial [glossary term] (inside the skull) target with gamma ray photons. The treated lesion is targeted and the patient's head immobilized (held completely still) through the use of an external metal frame attached to the skull by four screws. A large helmet-shaped

device with 201 separate, fixed "holes" or ports allows the radiation emitted by discrete (separate) radioactive cobalt-60 sources to enter the patient's head in small beams that converge on the designated target. The Gamma Knife is designed to treat intracranial targets only.

Advantages of the Gamma Knife include:

Over 30 years of clinical use with a large number of studies published in the medical literature

Targeting precision within 2 mm

Multiple targets in the brain are easily treated during a single treatment session

Disadvantages of the Gamma Knife include:

The basic design limits use to the brain only

The procedure for radiation targeting requires the placement of a somewhat painful stereotactic head frame

It can be difficult to treat patients with lesions located in certain areas (e.g. the periphery) of the brain

It cannot be used for staged radiosurgery (delivering the radiation dose in more than one fraction or treatment session); staged radiosurgery can be particularly beneficial for larger tumours or lesions located near nerves and other sensitive structures

Modified Linear Accelerator Systems

An alternative to the Gamma Knife was developed in the mid 1980s and utilized the conventional linear accelerators (linac) that are commonplace in most large hospitals. By combining a series of small modifications to the radiation delivery mechanism of the linac with specialized planning software, it is possible to do many types of brain radiosurgery. There are both dedicated and non-dedicated linac-based radiosurgery devices. Dedicated linac systems are used solely for radiosurgery treatment. In contrast, non-dedicated systems are the daily workhorses for conventional radiation therapy departments which can also be temporarily modified to perform radiosurgery. Compared to the latter multi-purpose linacs, dedicated systems tend to be more carefully calibrated for spatial accuracy and optimised for radiosurgical efficiency. Unlike the radioactive cobalt-based Gamma Knife, linac-based systems use X-ray beams generated from a linear accelerator. As a result, these devices do not require or generate any radioactive material. When treating brain tumours with linac radiosurgery, a metal head frame is attached to the patient's skull and used to precisely target the radiation beam. Common brand names for modified linacs include X-Knife (Radionics Inc).

Advantages of Multi-Purpose Linac Radiosurgical Systems include:

- More commonplace technology in hospitals

Disadvantages of Multi-Purpose Linac Radiosurgical Systems include:

- Less accurate

- Less efficient than dedicated systems, which results in longer treatment time

- Frame-based targeting only works for brain lesions

Shaped Beam Systems

The recent development of IMRT or Intensity Modulated Radiation Therapy has added another dimension to multi-fraction radiation therapy. These linac-based technologies use computer-controlled "beam-shaping" to do a better job of conforming the radiation dose to the shape of the tumour or other lesion. This form of advanced radiation therapy can be utilized at virtually any location in the body. IMRT technology enables a mechanical device (called a multi-leaf collimator) that is typically attached to most modern medical linear accelerators, to dynamically reshape the outlines and intensity of the radiation field during cancer treatment. When combined with sophisticated planning software, IMRT fits the dose of radiation to a target much better than conventional radiation therapy, and thereby minimizes the volume of surrounding normal tissue that is injured by treatment. While it appears that IMRT may produce fewer side-effects than conventional radiation therapy, IMRT is not as spatially precise as radiosurgery. Because of this imprecision, a full course of IMRT treatment is typically administered over multiple treatment sessions (typically 20-30+). Common brand names include X-Knife (Radionics) and Novalis (Brain Lab).

Advantages of Shaped-Beam systems include:

- The capacity to treat most regions of the body with IMRT

- When coupled to an invasive stereotactic frame, precision targeting for brain tumours that approaches, but does not equal, that of the Gamma Knife or CyberKnife®

- The capacity to more accurately target extracranial (non-brain) tumours than standard radiation therapy

An ability to deliver fractionated intracranial or extracranial treatment

Disadvantages of the Shaped Beam systems include:

- The need for an invasive head frame (similar to the Gamma Knife) to assure treatment accuracy when used for brain radiosurgery (single fraction)
- Less treatment accuracy when multiple fractions are used to treat areas of the brain where the use of an invasive head frame is impractical
- A significantly lesser degree of targeting accuracy when treating extracranial tumours compared to brain radiosurgery
Treatment accuracy is degraded further when the target moves during radiation delivery from either natural breathing or patient movement.