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

Meningiomas

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 meningioma?

Meningiomas make up approximately 15% of brain tumours. In 97% of cases, the tumour is benign, but in approximately 3% of cases, meningiomas can have malignant features. For the most part, meningiomas are slow growing and, as a consequence, can become quite large before they are detected. Most meningiomas go unnoticed until they cause a neurologic problem, either in the form of headaches or seizures, or in other instances, they can compress normal brain structures and cause a neurologic deficit. In an occasional patient, it is possible to establish that a meningioma has been present for five or ten years before discovery.

Meningiomas are believed to grow from the meningeal layer of membranes that is located between the skull and the brain, hence, the name of the tumour. Thus, even though meningiomas are classified as brain tumours, they are not located within brain tissue, but rather on the surface of the brain. Since the meningeal layer surrounds the entire brain, meningiomas can occur anywhere within the skull (or around the spinal cord, which also is surrounded by meninges). In some instances, meningiomas surround and entrap nerves and blood vessels, making their treatment more difficult. This is often the case for skull base meningiomas, since most of the critical arteries and nerves are located along the base of the skull.

Most meningiomas occur randomly in humans and the origins of this tumour are unknown. However, meningiomas have a familial origin in a small number of patients who suffer from genetic disorders such as neurofibromatosis or multiple meningiomatosis. Meningiomas are much more common in women (with a female to male ratio of 4:1), and older individuals with a peak incidence in the 50 to 70 year range. The female predominance and occurrence later in life has led some to believe that post menopausal changes in female hormones may somehow contribute to the growth of this tumour.

Treatment options for meningiomas

Treatment for meningiomas fall into four broad categories that include:

- Watchful waiting
- Surgical resection
- Conventional radiotherapy
- Stereotactic radiosurgery

Watchful waiting is the process by which a meningioma that has been discovered, is not treated, but rather carefully observed with serial MRI scans performed every 6 to 12 months. This is obviously not an option for patients with large symptomatic tumours. But since meningiomas are most often slow growing, and discovered when small, this is a reasonable option for elderly patients or those with significant medical problems. The main disadvantage of watchful waiting is that treatment of meningiomas becomes more difficult and risky as they increase in size.

Surgical resection has been the standard treatment for meningiomas for more than two generations and has many specific advantages. Most importantly, if the meningioma can be completely resected, and is confirmed to be benign, the cure rate is very high. Furthermore, surgery is uniquely able to provide tissue to a pathologist, who can generally unequivocally confirm the diagnosis of meningioma.

The obvious drawbacks to surgical resection are the not inconsequential risks of open surgery, which include bleeding, strokes, neurologic deficits, and infections. The complication rate of surgical resection is highest for meningiomas around the skull base. Furthermore, for many skull base meningiomas, a complete surgical resection is often not possible and the residual tumour is at great risk of re-growing over time.

Conventional radiotherapy - There are basically two types of radiation that are used to treat meningiomas:

1) conventional radiotherapy and

2) stereotactic radiosurgery.

Conventional radiotherapy is generally used in the treatment of malignant meningiomas, which are often diffuse and hard to localize, or when treating meningiomas that are too large for radiosurgery. For most meningiomas, treatment with conventional radiation is not as aggressive or successful as radiosurgery, and therefore, represents a second line of therapy.

Stereotactic radiosurgery administered with the CyberKnife® is one of the most advanced methods for treating meningiomas. During radiosurgery, a highly focused, precisely targeted beam of radiation is used, almost like a surgeon's scalpel, to deliver a lethal dose of energy to the tumour, while sparing normal brain tissue adjacent to the tumour. The success rate with stereotactic radiosurgery is very high, with approximately 95% of radiosurgically treated meningiomas dying after one or a small series of "staged" treatments.

Like any surgical treatment, radiosurgery has risks. These include a small chance that the tumour will continue to grow despite treatment, and a small risk of radiation injury to normal nerves immediately adjacent to the tumour. Overall, these risks are low, typically being substantially less than the microsurgical resection of such a meningioma. This is especially true for skull base lesions.

When is radiosurgery not the best option for meningiomas?

There are several instances where radiosurgery is not the best option for treating meningiomas. For example, large meningiomas are difficult to treat with radiosurgery since the risk of delivering radiation is substantially higher than that for small tumours.

While each case must be evaluated individually, most radiosurgery centres are reluctant to treat meningiomas larger than 3.5 cm in diameter; volume is ultimately a more important factor than any one dimension of the tumour. Furthermore, larger meningiomas often compress the brain and produce symptoms.

Surgical resection is uniquely able to promptly decompress the brain and restore neurologic function. Moreover, if there is some suspicion that the tumour being evaluated is not a meningioma, then your surgeon may recommend a biopsy or surgical resection itself so that a definitive diagnosis can be made.

A drawback of radiosurgery is that it destroys the tumour without establishing a pathologic diagnosis. Therefore, a surgeon must be reasonably confident of the diagnosis based on imaging studies alone (MRI or CT), to recommend radiosurgery as a first-line treatment. Obviously, among patients who have had a prior surgical resection and there was either residual meningioma left behind, or the tumour recurred, it is generally not necessary to biopsy a tumour again prior to CyberKnife® radiosurgery.

The results of meningioma radiosurgery

Most medical centers report excellent tumor control rates after radiosurgery, on the order of 90 to 95%. The risk of neurologic injury depends on location.

For non-skull base meningiomas, the risk of temporary radiation injury is on the order of 2-3% and the risk of permanent radiation injury on the order of 1%. These complication rates are slightly higher for larger lesions and skull base meningiomas.

If patients have clinical symptoms, such as headaches, double vision, seizures, etc., there is a significant likelihood that these will improve after radiosurgery. However, such improvement typically takes place over many months or even years.

The advantage of CyberKnife® radiosurgery for meningiomas

The CyberKnife® is a particularly advanced form of radiosurgery. An important advantage for the patient is that no metal frame is screwed into the skull, which enables the operation to be much less painful than other radiosurgical systems.

Although it is non-invasive, the CyberKnife® has been proven to be very accurate; it delivers beams of radiation to an accuracy of approximately 1 mm. This measure of precision is at least as good, if not better, than standard frame-based linear accelerators and the Gamma Knife (See references: Chang and Maciunas).

Another significant advantage of the CyberKnife® frameless approach is that staged (fractionated) treatment is readily possible. In selected cases, there are advantages to administering the radiation over two to five smaller doses, instead of one large dose. This procedure, which is sometimes termed fractionated stereotactic radiosurgery (FSR), makes it possible to more safely treat some larger meningiomas, or those immediately next to critical structures, like the vision (optic) nerve.

Most common meningioma locations

While meningiomas have a wide variety of locations, the following are the most common locations:

1. Cavernous sinus meningioma: These meningiomas are located in a region called the cavernous sinus, and often are wrapped around critical nerves that control eye movement and feeling in the face. Tumours in this location are extremely difficult, if not impossible, to remove with microsurgery because of the appreciable risk of permanent neurological injury (see reference: Chang). Patients with this type of meningioma often present with double vision, headaches, and numbness in the face.

2. Optic nerve meningioma: These meningiomas occur in and around the optic nerve and, depending on the location of the tumour, usually present with visual loss in one or both eyes. Surgery on these meningiomas is fraught with difficulty, and blindness is a frequent complication of open surgery. Because these tumours are oftentimes inseparable from the optic (vision) nerve, a single radiosurgical treatment also has a very high risk of blindness. Therefore, the typical one-time treatment with a frame-based radiosurgical device cannot be used in such cases. However, with the CyberKnife®, we have been able to treat these tumours using a staged treatment with excellent overall results.

3. Tentorial meningioma: This type of meningioma is located along a "meningeal" structure deep in the brain termed the tentorium. If such tumours are located along the medial edge of the tentorium, they can surround important cranial nerves. However, more commonly they involve the lateral tentorial edge, where the tumour can be wrapped around large veins called sinuses. Common presenting symptoms for these tumours include headaches, seizures, and in rare instances, double vision.

4. Cerebellopontine angle (CPA) meningioma: These meningiomas often mimic acoustic neuroma, since both tumour types are located in what is called the cerebellopontine (CPA) angle. Smaller tumours present with either facial numbness or weakness as well as hearing loss. Larger CPA meningiomas compress the brainstem and cerebellum (the balance portion of the brain at the back of the head), resulting in balance problems, dizziness, or frequent falls.

5. Foramen magnum meningioma: These meningiomas occur at the base of the skull where the top of the spinal cord is located. They generally cause their symptoms by compressing the brainstem or upper spinal cord. Primary symptoms include a hoarse voice, swallowing difficulties, balance problems, or weakness and numbness in the arms and legs.

6. Olfactory groove meningioma: These are located at the front of the skull base next to the olfactory (smell) nerves. Primary symptoms include loss of smell or, in rare instances, leakage of spinal fluid from the nose.

7. Sellar meningioma: These tumours are located within an area of the skull known as the sella turcica that is adjacent to the pituitary gland. Primary symptoms of such tumours include headaches, visual loss if there is compression of the optic nerves, hormonal changes if there is compression of the pituitary gland, or motor or sensory deficits if there is compression of the brainstem.

8. Convexity meningioma: Such meningiomas are located along the top of the brain, an area referred to as the convexity of the skull. Primary symptoms can include headaches, seizures, or weakness or numbness in the arms or legs (usually along one side). In most patients, this type of meningioma can be removed through conventional open microsurgery with low risk. However, in elderly patients, or patients with multiple medical problems, it may be preferable to treat meningiomas in this location with radiosurgery.

What tests/studies are needed prior to CyberKnife® radiosurgery for meningiomas?

For most meningiomas, an MRI scan is the only study that is needed before various treatment alternatives can be considered. However, certain meningiomas are located in regions which cause symptoms that warrant additional testing. For example, cerebellopontine angle meningiomas can, in some instances, cause hearing loss. For meningiomas in this location, a hearing test, or audiogram, in addition to the head MRI scan, is advisable. Oftentimes, optic nerve meningiomas present with visual loss.

Therefore, when such tumours are suspected, a formal ophthalmologic visual field test is recommended. Sellar meningiomas can cause hormonal changes or be confused with pituitary tumours, so patients with tumours in this location should have serum hormone studies prior to opting for radiosurgery or any other surgery.

Even though meningiomas grow slowly, it is optimal to have an MRI scan within three months of treatment. An up-to-date scan ensures the best possible comparison of tumour size before and after CyberKnife® radiosurgery.

What can I expect after meningioma CyberKnife® radiosurgery?

Since radiosurgery is an outpatient procedure, the vast majority of patients experience no side-effects. It usually takes six to twelve months after the radiosurgery for the meningioma to begin to die.

Therefore, patients are typically followed postoperatively with serial MRI scans periodically. A common protocol is an MRI scan every six months for the first two years, then once a year for the next two years, and then every two to three years thereafter.

Radiosurgery destroys the tumour cells and turns the tumour into scar tissue. This means that there is typically a visible scar in the MRI scan at the site where the tumour was first located. Such a scar will show up for many years on MRI scans, and is often visually indistinguishable from the original tumour, except for the fact that it gradually shrinks over time. However, not uncommonly, there will be no change in the size of a tumour after radiosurgery, even after several years.

This does not mean that the radiosurgery is not effective, but just that the tumour turned into scar tissue without much shrinkage. In other instances, the tumour can shrink significantly after radiosurgery. It is critical that any meningioma patient who is considering radiosurgery be thoroughly aware of this fact. Radiosurgery is the wrong procedure for any patient that expects the tumour to suddenly vanish on the postoperative MRI scan.

Most patients feel great and are without any symptoms after radiosurgery. In rare instances, a patient can experience mild headaches or dizziness during the first 24 hours after treatment. Other side-effects are quite rare.

References

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3. Chang SD, Adler JR Jr, Martin DP: LINAC radiosurgery for cavernous sinus meningiomas. Stereotactic and Functional Neurosurgery. 1998: 71(1): 43-50.

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.