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

Pituitary Adenoma

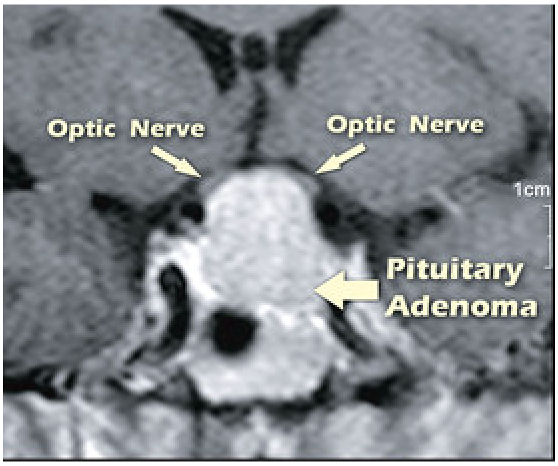
IMPORTANT NOTE

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 Pituitary Adenoma?



The pituitary is the master control centre of hormones in the body. It sits in a crevice called the sella turcica at the base of the skull. This location puts it right under the optic chiasm, which is the crossing point of the two vision nerves (optic nerves). The normal pituitary gland produces several important hormones: adenocorticotrophic hormone (ACTH) stimulates the adrenal gland; thyroid stimulating hormone (TSH) stimulates the thyroid gland; luteinizing hormone and follicle stimulating hormone (LH and FSH) interact with the sexual organs; growth hormone (GH) is involved with sugar metabolism and cell growth; and prolactin (PRL) affects lactation.

Pituitary adenomas are slow growing, benign tumours of the pituitary gland. They represent 10-15% of all brain tumours. Those that are small (less than 1 cm in largest diameter) are called microadenomas, while larger tumours (greater than 1 cm) are commonly called macroadenomas. Pituitary tumours can also be divided into functioning and non-functioning tumours. As the classification implies, functioning tumours produce hormones, often in large, unregulated amounts. Correspondingly, non-functioning tumours do not produce significant amounts of hormones.

What are the presenting symptoms of pituitary adenoma?

Symptoms from pituitary adenomas can be classified as follows:

1) Overproduction of hormones: The specific symptoms experienced by a patient will depend on the type of hormone that is being overproduced. A tumour that produces large amounts of ACTH causes Cushing Disease, which leads to obesity, high blood pressure, and muscle weakness, among other symptoms. A prolactinoma is a pituitary adenoma that produces large amounts of prolactin. Symptoms of this include irregular menstruation,

sexual dysfunction and breast discharge. A growth hormone producing tumour leads to acromegaly, a condition characterized by progressive enlargement of hand and foot size and an alteration of facial features.

2) Hypopituitarism: A non-functioning adenoma can still lead to hormonal problems. It does so by compressing the pituitary gland and results in a decrease or cessation of normal hormone production by this organ.

3) Visual deficit: A large tumour can grow upwards, out of the sella turcica and compress the optic nerves (optic chiasm). Frequently, this leads to a specific form of "tunnel vision" called bitemporal hemianopsia.

4) Non-specific symptoms: Sometimes a sizable pituitary adenoma can lead to headaches or a sensation of pressure or fullness behind the eyes. Rarely, bleeding into a tumour can lead to severe headache, double and blurring vision (pituitary apoplexy).

Diagnostic Studies

Any patient suspected of having a pituitary adenoma must undergo at least two tests. The first is a magnetic resonance scan (MRI), with specific views of the sella turcica. This test provides the anatomic information to determine whether there is compression of the optic chiasm or invasion of neighbouring structures, such as the cavernous sinus. The second test is a full endocrinological evaluation to determine whether hormone levels have been affected by the tumour. If the tumour is large, then a visual evaluation, including a visual field examination, becomes important. This last test will reveal whether the tumour has affected the optic nerves or chiasm.

Treatment Options

Medical treatment is available for pituitary adenoma that overproduce prolactin and growth hormone. For prolactinoma, bromocriptine is quite effective in lowering prolactin levels in a patient's blood and shrinking the tumour. Acromegaly, caused by an overproduction of growth hormone, can be treated with octreotide. However, growth hormone secreting tumours rarely respond as well to octreotide as prolactinomas do to bromocriptine treatment.

For all other symptomatic adenomas, the "gold-standard" therapy is surgical removal of the tumour. The goal of surgery is to resect as much of the tumour as is safe, thereby eliminating pressure on the optic structures, and removing those cells that are overproducing hormone. Most pituitary surgeries do not require cutting on the scalp and drilling into the cranium. Instead, the most common surgical approach is called "transsphenoidal," because the surgery is performed through the sphenoid sinus, which is an air-filled space behind the nose. The incision is made either under the lip or inside the nose. By working behind the region of the nose and attacking the tumour from underneath the sella turcica, the tumour can be removed. An endoscopic-assisted variant of the transsphenoidal procedure is becoming increasingly popular. This method of resecting pituitary adenomas is less invasive. It utilizes a small endoscope to provide a surgeon with a small but adequate view of the operative site. With this later operation, hardly any incision at all is needed.

The major risks of transsphenoidal surgery include injury to the carotid arteries on either side of the tumour, the optic chiasm on top of the tumour, and to the normal pituitary gland, which can often be indistinguishable from the tumour. When the normal pituitary gland does not function properly after surgery, the patient may require life-long hormone replacement.

Not all patients with pituitary tumours need treatment. Sometimes, an "incidental" pituitary microadenoma is discovered on an MRI scan done for other reasons. In such a case, a period of observation is a reasonable alternative approach. Treatment may only be needed when the microadenoma demonstrates that it enlarges with time.

Radiation Treatment and Radiosurgery

If surgery is unable to remove the entire tumour, then radiation treatment may be necessary to control the tumour and prevent it from growing. Radiation may also be an option for patients who are medically unsuitable for surgery or do not want to have surgery.

Conventional radiation treatment directs a small number of radiation beams towards the entire region around the sella turcica and pituitary gland. This technique results in a significant margin of normal tissue being included in the "treatment field". To compensate for this fact, conventional radiation treatment is given in daily doses over several weeks. Such therapy is generally very effective in preventing the tumour from growing. For hormone-producing tumours, it is also effective in gradually lowering the hormone levels over many years. Despite the fact that with conventional radiotherapy the optic chiasm receives as much radiation as does the tumour, the risks of visual complications are very low. However, the same cannot be said about normal hormonal function. Since both the pituitary and the hypothalamus (another important hormone control centre) receive radiation during treatment, nearly half the patients treated with conventional radiation will eventually develop abnormally low hormone levels (hypopituitarism).

Radiosurgery is a new option for treating pituitary adenoma. By focusing the radiation on only the tumour, this form of treatment minimizes the anatomical spread of radiation to normal brain. Emerging data indicates that radiosurgery may be more effective than conventional radiation in lowering abnormal hormone production, and does so over a shorter time interval.

Most radiosurgery techniques, like surgery itself, require treatment to be delivered as a one-time procedure. However, some of the unwanted side-effects of radiation, including the most feared, visual loss, may be accentuated by delivering the radiation all in one day rather than over several sessions; this risk of radiation injury is greatest in those patients where the pituitary is close to or actually involves the optic chiasm or hypothalamus. In higher risk patients, the risk of injury to critical brain structures may be reduced by staging the radiosurgical ablation.

Benefits of CyberKnife® Radiosurgery

CyberKnife® radiosurgery treatment of pituitary adenoma melds the advantages of both conventional radiation and radiosurgery. Since it is radiosurgery, the area targeted for treatment is minimized to the region of the adenoma only. Perhaps even more importantly, CyberKnife® radiosurgery can be delivered in divided doses just like conventional radiation. Such treatment is termed fractionated stereotactic radiotherapy (FSR) or staged radiosurgery.

This approach further lessens the radiation risk to the sensitive structures around the tumour, such as the optic chiasm and hypothalamus. CyberKnife® fractionated stereotactic radiotherapy is also well-suited for treating a pituitary adenoma that has invaded the cavernous sinus on either side of the sella turcica. The cavernous sinus contains nerves that control eye movement and facial sensation. Because the nerves traverse the field of radiation, fractionated treatment may lessen the risk to those nerves.

Who should get CyberKnife® Radiosurgery?

As discussed above, there is a subset of patients with pituitary adenoma that is particularly suited to undergo CyberKnife® radiosurgery:

1) Patients with small tumours that overproduce a pituitary hormone

2) Patients who have residual tumour after transsphenoidal surgery

3) Patients with hormone-producing tumours, who continue to have higher than normal hormone levels after surgery

4) Patients with adenoma that has invaded the cavernous sinus

5) Patients who are either unwilling or unable to have transsphenoidal surgery.

References

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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.