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

Pancreatic Cancer

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 pancreatic cancer?

Pancreatic cancer is an abnormal growth of malignant cells that originates from one of the many parts of the pancreas. The pancreas, a 6-inch organ located behind the stomach in the upper abdomen, produces both enzymes for digesting food and hormones, such as insulin, that regulate multiple bodily functions.

Because the pancreas is composed of a variety of cell types, there are many forms of pancreatic cancer. Unfortunately the most common pancreatic cancer, adenocarcinoma (which arises from the pancreatic duct and gland cells), is also the most difficult to treat. Pancreatic adenocarcinoma, which comprises approximately 95% of all pancreatic cancer, is the main reason there are almost as many deaths from pancreatic cancer each year as there are newly diagnosed cases (about 30,000 each year). The survival rate is generally better for the 5% of pancreatic cancers that are not adenocarcinomas.

There are basically two reasons why pancreatic cancer is so difficult to cure. First, it grows silently with very few symptoms until the tumour is quite advanced or has already spread outside of the pancreas. Secondly, this type of cancer generally does not respond well to many of the available treatments.

What are the symptoms associated with pancreatic cancer?

The earliest signs of pancreatic cancer are often so vague and mild that they are overlooked. The most common early symptoms typically include loss of appetite with mild weight loss and a vague, mild discomfort in the upper abdomen or occasionally in the middle-back area (the pancreas is positioned in the back of the abdomen directly over the spine). Because there are so many other potential, and relatively minor, explanations for this spectrum of symptoms, the earliest signs of pancreatic cancer are often ignored. However, as the cancer progresses, it causes increasingly more noticeable symptoms, such as yellow jaundice (often with little or no associated pain), which stems from the obstruction of the main duct that drains the liver's bile. As the tumour continues to grow, other digestive problems such as bloating or nausea from obstruction of the stomach are also common. Although pancreatic cancer is difficult to detect on physical exam in initial stages, firmness is some times felt in the upper middle abdomen late in the course of the disease.

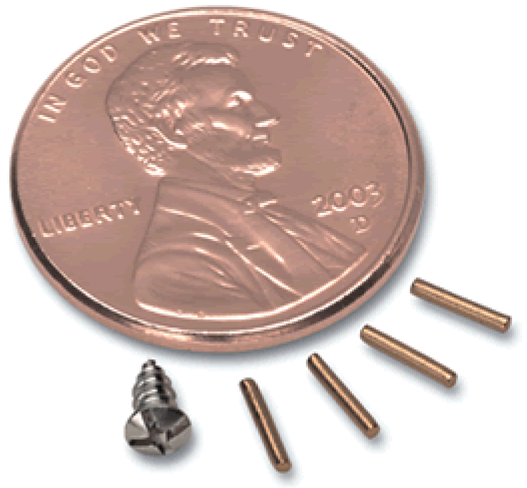
How is pancreatic cancer diagnosed?

Despite ongoing research to diagnose pancreatic cancer earlier, no effective blood test has been developed to screen for this cancer. Although the presence of blood tumour marker "CA 19-9" may sometimes be used to help confirm a diagnosis of pancreatic cancer or follow a patient after treatment, this relatively simple test has not proven effective as a screening tool. Instead, radiologic tests such as an abdominal ultrasound or CAT scans are used to arrive at a presumptive diagnosis of pancreatic tumour. A definitive diagnosis of pancreatic cancer is most frequently established through subsequent endoscopy and appropriate biopsies. During endoscopy, a lighted fibre-optic tube is passed through a patient's mouth and into the stomach and duodenum (upper intestine).

Using an ultrasound probe, it is sometimes possible to biopsy the tumour under direct visualization. The endoscope allows a specially trained doctor to visually inspect this portion of the gastrointestinal tract as w ell as the region in and around the junction with the pancreatic duct. In those patients who suffer from jaundice, a special tube called a stent will oftentimes be inserted into the bile duct at the time of endoscopy to open up this passageway and thereby permit more normal drainage of bile. It is not unusual to use all three of these tests (CAT scan, ultrasound, and endoscopy) when working up suspicious symptoms. Another frequently used method of diagnosis is to pass a needle into the tumour using a CAT scan to direct the placement of the needle. A small sample of the tumour is removed by this method and visualized under a microscope to confirm the presence of a tumour and to identify the type of tumour.

What treatment options are available?

Treatment for pancreatic cancer, as with all cancers, may involve a combination of surgery, radiation, and chemotherapy. To determine the best option(s) for an individual, the cancer is first evaluated and "staged". Staging determines how far a cancer is believed to have spread from its site of origin. Early stages generally have a more favourable prognosis and a much better chance of cure. Unfortunately, most pancreatic cancers when diagnosed usually already display some evidence of either growing into the organs directly surrounding the pancreas ("local invasion"), or have spread to other body sites away from the pancreas ("metastasis"). Metastases can occur to nearby lymph nodes or to more distant sites such as the liver or lining of the abdominal cavity. Treatment for such advanced cancer is rarely successful. In most advanced cases, much of the current treatment is directed at simply making patients more comfortable and improving quality of life.



For earlier stage malignancies, and especially those without metastatic disease, surgical resection (removal) through a procedure called a "pancreaticoduodenectomy" or "Whipple procedure" has been the mainstay of pancreatic cancer treatment. Despite the difficulty and risk associated with this surgery, it has been considered the only real chance for curing pancreatic cancer and offers the best chance of long-term survival. However, some patients with tumours confined to the pancreas are not good candidates for this procedure. If the cancer appears to involve critical blood vessels going to the small bowel (the superior mesenteric arteries), this operation is not feasible. Other patients may have serious medical problems that prohibit such a major operation.

In general, only a small percentage of all pancreatic cancer patients qualify as candidates for surgery, and many receive surgery only as a palliative measure (to relieve symptoms and make them more comfortable). Nevertheless, recent advances in other treatment modalities, such as radiation therapy and chemotherapy, have lead to other promising therapies, especially in situations where the pancreatic tumour cannot be removed surgically. One such development is the use of stereotactic radiosurgery to treat pancreatic tumours.

What is CyberKnife® stereotactic radiosurgery and how might it help patients with pancreatic cancer?

Stereotactic radiosurgery is a technique for delivering highly accurate, very large focused doses of radiation to tumours while minimally irradiating surrounding normal tissues. (See What is Stereotactic Radiosurgery section for additional information.) Radiation oncologists and neurosurgeons have been using this technique for almost two decades to effectively treat brain tumours. Improvements in targeting and radiation delivery now allow physicians to treat tumours outside the brain with radiosurgery for the first time. In particular, some radiation oncologists and surgeons are using CyberKnife® radiosurgery to treat abdominal tumours. The aggressive doses of focused radiation utilized in pancreatic cases are similar to those that have been shown in prior studies to be very effective in destroying brain and spinal tumours. Multi-institutional clinical studies are presently underway to test the effectiveness of CyberKnife® radiosurgery for treating localized, non-metastatic pancreatic cancer. Preliminary studies conducted at Stanford University Medical Centre in patients with relatively advanced disease suggested that CyberKnife® radiosurgery was both well tolerated and that treatment was associated with some clinical benefit.

What is the patient process for pancreatic radiosurgery using the CyberKnife®?

Prior to radiosurgery, 3-5 small gold seeds are implanted in the tumour to serve as fiducial markers

These markers are visible to normal diagnostic x-rays and are tracked by the CyberKnife® to determine the precise position of the tumour throughout radiosurgery. The markers are placed through a needle under CT guidance by an interventional radiologist in an outpatient procedure that takes about 1 hour.

Approximately 1 week after the seeds are placed, a treatment planning session is scheduled. At this time, a custom mould (called an alpha cradle) will be made to hold the body in place during the radiosurgery. Next, a specialized pancreatic protocol CT scan will be completed with the patient lying in this custom alpha cradle. The CT images are downloaded to a treatment planning computer and a customized radiosurgery plan is developed according to each patient's anatomy and the shape/location of the tumour.

A team including a radiation oncologist, a pancreatic surgeon, an interventional radiologist, a diagnostic radiologist, a physicist, an oncology nurse, and a radiation therapy technician will all be involved in different aspects of patient care. Bringing together a team of highly trained individuals with different areas of expertise will benefit patients by providing them with the highest quality of care possible.

On the day of radiosurgery, patients receive an anti-nausea pill to take 1 hour before the scheduled treatment. The actual radiosurgery procedure takes place over a period of 3-5 hours. Patients are allowed to eat a normal meal and take all of their normal medications. Following radiosurgery treatment, patients are instructed to eat a light dinner and take another anti-nausea pill later in the evening.

What are the side effects of CyberKnife® treatment?

In patients that have been treated thus far, the majority have no side effects related to radiosurgery. They are able to carry out all of their normal activities without interruption. In a minority of patients (approximately 10%), transient episodes of mild nausea and increased abdominal pain have been reported. These symptoms, which all responded successfully to medication, lasted less then 24 hours and all resolved spontaneously.

What results have been seen with CyberKnife® radiosurgery for pancreatic tumours?

In a recently completed study at Stanford University Medical Centre, patients were treated with radiosurgery using a "low," "middle," and "high" radiation dose. In 100% of patients treated at the "high" dose, all patients had their pancreatic tumours controlled for the remainder of their lives. In other words, these tumours either stopped growing or decreased in size following radiosurgery. In most patients, there was also a corresponding decrease in the level of detectable CA 19-9 (serum tumour marker for pancreatic cancer).

None of these patients suffered any significant treatment-related acute toxicity. As an unexpected benefit, most patients who had pain prior to radiosurgery had a decrease in their pain within a few weeks following treatment. Some patients had such dramatic reduction in their pain that they were able to stop taking all pain medications. Radiosurgery for pancreatic cancer has had a significant impact on improving the quality of life for these patients.

Are there clinical trials with the CyberKnife® available?

Yes. Stanford University Medical Centre has recently opened a phase II study for pancreatic cancer patients with locally advanced/unresectable (inoperable) tumours. Eligible patients must have tumours that have not spread beyond the pancreas. In this study, patients will be treated with conventional chemoradiotherapy followed by radiosurgery to the pancreatic tumour. Following this treatment, patients will be restaged (re-assessed) and can receive either additional chemotherapy or undergo surgical resection if their tumour regresses enough to be removed surgically.

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.