

Intraocular Malignant Melanoma

Furdova Alena^{1*}

¹Department of Ophthalmology, Comenius University, Faculty of Medicine, Hospital Ruzinov, Slovak Republic

***Corresponding author:** Furdova Alena, Department of Ophthalmology, Comenius University, Faculty of Medicine, Hospital Ruzinov, Slovak Republic, Tel: +421 2 48234 607; Email: alikafurdova@gmail.com

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UVEAL MELANOMA

Melanoma of the uveal tract (iris, ciliary body, and choroid), is the most common primary intraocular malignancy in adults. Uveal Melanoma (**UM**) is diagnosed mostly in older age, with a progressively rising age-specific incidence rate that peaks near the age of seventy. Ocular melanoma is likely to metastasize in other regions of the body such as liver, breast, lung, and kidney. Factors associated with the development of this tumor include genetic factors, race, color of the eyes, fair coloring of the skin and the ability to tan. Many observational studies have attempted to explore the relationship between exposure to the sunlight and risk of uveal melanoma [1,2].

The comparatively low incidence of iris melanomas has been attributed to the characteristic features of these tumors. Usually, uveal melanomas are in early stages of their development completely asymptomatic. Iris melanomas rarely metastasize. Choroidal melanoma is the most common ocular melanoma- comprising over 75 % of all intraocular melanomas. Posterior uveal melanomas are cytologically more malignant, and metastasize more frequently than iris melanomas. Typically, choroidal melanoma is a brown, elevated mass, and the degree of its pigmentation ranges from dark brown to totally amelanotic. Usually, uveal melanomas are in early stages of their development completely asymptomatic.

In advanced stages the symptoms are dependent on tumor location. The most important test to establish the presence of intraocular melanoma is the examination by an experienced clinician. Diagnostic testing can be extremely valuable in establishing and confirming the diagnosis. Prognosis can be influenced by number of factors. The most important are the type of cells, the size of tumor, the margins location of the tumor, karyotype and its extraocular extension. Cell type, however, remains the most often used predictor of outcome. The treatment depends on the site of origin (choroid, ciliary body or iris), the size and location of the lesion, the age of the patient and whether extraocular invasion, recurrence or metastasis has occurred. Extraocular extension, recurrence, and metastasis are associated with an extremely poor prognosis and long-term survival cannot be expected.

Alternative treatment modalities have been proposed in recent years including enucleation, local resection, plaque brachytherapy, charged-particle radiotherapy, stereotactic photon beam irradiation therapy, transpupillary thermotherapy and photodynamic therapy.

Over the past three decades diagnostic methods have improved and radiotherapy (external beam, charged particle or brachytherapy) has become the preferred treatment for most of the patients with uveal melanoma. The desire to improve survival and preserve vision in patients with uveal melanoma has stimulated the development of alternative therapies. Different radiation modalities are currently in use in treatment of posterior uveal melanoma. One of the methods of “conservative” approach is the Stereotactic Radiosurgery (**SRS**) by linear accelerator [3].

OVERVIEW OF METHODS OF TREATMENT OF UVEAL MELANOMA

Nowadays there are many more treatment options besides enucleation, which was the only option for most of last century [1]. The more conservative treatment options aim to spare the affected eye and retain vision. Treatment of uveal melanoma depends on various factors including age of the patients, systemic health of the patient, condition of the opposite eye, tumor size and location. In general small and medium melanomas may be treated with Transpupillary Thermotherapy (**TTT**), plaque radiotherapy combined with TTT, proton beam or stereotactic radiotherapy.

Large melanomas are usually treated with enucleation while in some cases proton beam radiotherapy or stereotactic radiotherapy is indicated. With stereotactic radiotherapy several large dose fractions are given to reduce the side effects of radiotherapy and gain an optimal result in tumor control. Reduction of side effects and improvement of the therapeutic ratio can be achieved with a better understanding of the radiosensitivity and capacity for DNA damage repair of these tumors. Smaller fraction doses and consequent smaller high-dose volumes are justified to optimize dose and fractionation. Fractionated stereotactic irradiation has a challenging potential as an eye-preserving treatment in uveal melanoma [4].

Nevertheless, metastases cannot be prevented. Based on theoretical models, clinically manifest metastases are likely to occur 5 or 6 years after onset of the systemic dissemination.

At the time that uveal melanoma is diagnosed, micrometastases may have been spread already. Therefore, metastatic disease occurring after treatment is not uncommon. Approximately half of the patients will die from the disease within 10 to 15 years of enucleation. Once a metastasis is discovered the survival is less than 7 months. If a metastasis arises as a solitary lesion in the liver, increased survival may be obtained by local resection of the lesion. Furthermore, there have been reports on tumor regression after treatment with hepatic arterial chemo-embolisation, isolated hepatic perfusion with high-dose melphalan and a combination of chemo-immunotherapy in the BOLD study. These therapies may prolong survival, but they will not cure the patients. Enucleation induced metastases may occur through manipulation of the eye during treatment, as was demonstrated in animal studies.

Pre-enucleation radiotherapy, aimed at reducing enucleation induced metastases, proved to be effective in animal models. However, it is not applied at present since clinical studies did not show any survival benefit.

Despite diagnostic advances the rate of metastatic disease is still not reduced, making it more important to find alternative treatments for metastases in particular [4].

Treatment by Location and Size

The location and size of the tumor are considered as two of the main factors in determining treatment for eye melanoma. There is no point in saving an eye if a small melanoma in a crucial place has completely destroyed vision. It is important to keep in mind - patients who have had enucleation and those who have had radiation therapy respond similarly when asked about the quality of their lives after treatment. The most important for them was the survival of the tumor.

Treatment by Stage

The treatment options, that are applicable to a patient, depend on factors such as:

- Location of tumor in the eye
- Metastasis of the tumor
- Age and general status of the patient.

Therapy of iris melanoma is not indicated if the tumor is small and it does not grow. But if the tumor begins to grow or is symptomatic, treatment may involve:

- Internal radiation therapy by help of small implants
- Surgical excision of the tumor
- Enucleation of the eyeball
- Treatment of ciliary body melanoma may include:
 - Internal radiation therapy using small implants
 - External-beam radiation therapy

- Excision of the tumor
- Enucleation of the eyeball.

Treatment of small choroidal melanoma - if the small tumor begins to grow, or is symptomatic, treatment may involve:

- Laser therapy (photocoagulation or thermotherapy)
- Internal radiation therapy using small implants
- External-beam radiation therapy
- Removal of the tumor and part of the iris or choroid
- Enucleation of the eyeball
- Treatment of medium size and large choroidal melanoma may include:
 - Internal radiation therapy using small implants
 - External-beam radiation therapy
 - Internal radiation therapy followed by laser therapy (coagulation or thermotherapy)
 - Removal of the tumor and part of the iris or choroid
 - Enucleation of the eyeball.

Treatment of recurrent intraocular melanoma will depend on factors such as:

- Therapy the patient received in the past
- Patient's age and his/her health state
- Location where the recurrent tumor appeared
- Localization and shape of the relapsed tumor.

RADIATION THERAPY

Radiation therapy is a common therapy for intraocular melanoma that uses high energy radiation to kill tumor cells. Radiation therapy can often preserve some vision, although sometimes this is lost anyway because radiation damages other parts of the eye. The eye structure is preserved and that is the main advantage of this type of therapy.

There are two categories of radiation therapy: external radiation therapy that uses a machine outside the body to send radiation toward the tumor, and internal radiation therapy that uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the tumor. The way the radiation therapy is given depends on the type and stage of the tumor being treated.

In ophthalmooncology field we use both photon beam irradiation and also proton beam irradiation [5-7].

Mechanism of Action

The fundamental principle of radiosurgery is that of selective ionization of tissue, by means of high-energy beams of radiation.

Ionization is the production of ions and free radicals which are usually deleterious to the cells. These ions and radicals, which may be formed from the water in the cell or from the biological materials, can produce irreparable damage to DNA, proteins, and lipids, resulting in the cell's death. Thus, biological inactivation is carried out in a volume of tissue to be treated, with a precise destructive effect. The radiation dose is usually measured in grays, where one gray (**Gy**) is the absorption of one joule per kilogram of mass. A unit that attempts to take into account both the different organs that are irradiated and the type of radiation is the Sievert, a unit that describes both the amount of energy deposited and the biological effectiveness.

According to a December 2010 article in The New York Times, radiation overdoses have occurred with the linear accelerator method of radiosurgery, in large part due to inadequate safeguards in equipment retrofitted for stereotactic radiosurgery. The U.S. Food and Drug Administration (**FDA**) regulate these devices, whereas the Gamma Knife is regulated by the Nuclear Regulatory Commission. This article focuses on Varian equipment and associated software, but the problem is not likely limited to that manufacturer [1].

Types of Radiation Source

The selection of the proper kind of radiation and device depends on many factors including lesion type, size and location in relation to critical structures. Data suggests that similar clinical outcomes are possible with all of the various techniques. More important than the device used are issues regarding indications for treatment, total dose delivered, fractionation schedule and conformity of the treatment plan. The fundamental principle of radiosurgery is that of selective ionization of tissue, by means of high-energy beams of radiation.

Radiosurgery is indicated primarily for the therapy of tumors, vascular lesions and functional disorders. Significant clinical judgment must be used with this technique and considerations must include lesion type, pathology if available, size, location and age and general health of the patient. General contraindications to radiosurgery include excessively large size of the target lesion or lesions too numerous for practical treatment. Patients can be treated within one to five days and on an outpatient basis. By comparison, the average hospital stay for a craniotomy (conventional neurosurgery, requiring the opening of the skull) is about 15 days. Radiosurgery outcome may not be evident until months after the treatment. Since radiosurgery does not remove the tumor, but results in a biological inactivation of the tumor, lack of growth of the lesion is normally considered to be treatment success.

Safety Ensured

Patient safety is very important and is assured in several ways. Radiosurgery is performed by a multidisciplinary team of radiation oncologists, neurosurgeons, neurodiagnostics and medical physicists to operate and maintain highly sophisticated, highly precise and complex instruments, like medical LINACs and the Gamma Knife. The highly precise irradiation of targets within the brain and spine is planned using information from medical images that are obtained via computed tomography, magnetic resonance, and angiography. Before treatment is delivered to the patient, the treatment plan is developed and approved by the radiation oncologist in collaboration with the radiation dosimetrist and physicist. The plan is double-checked before treatment is given and quality-control procedures ensure that the treatment delivered is the same as was planned. Quality control of the linear accelerator is also very important. There are several systems built into the accelerator so that it will not deliver a higher dose than the radiation oncologist has prescribed. Each morning before any patients are treated, the radiation therapist performs checks on the machine using a piece of equipment called a “tracker” to make sure that the radiation intensity is uniform across the beam and that it is working properly. In addition, the radiation physicist conducts more detailed weekly and monthly checks of the linear accelerator.

Modern linear accelerators also have internal checking systems to provide further safety so that the machine will not turn on until all the treatment requirements prescribed by your physician are perfect. When all the checks match and are perfect, the machine will turn on to provide your treatment. During treatment the radiation therapist continuously watches the patient through a closed-circuit television monitor. There is also a microphone in the treatment room so that the patient can speak to the therapist if needed. Port films (X-rays taken with the treatment beam) or other imaging tools are checked regularly to make sure that the beam position doesn't vary from the original plan.

Safety of the staff operating the linear accelerator is also important. The linear accelerator sits in a room with lead and concrete walls so that the high-energy X-rays are shielded. The radiation therapist must turn on the accelerator from outside the treatment room. Because the accelerator only gives off radiation when it is actually turned on, the risk of accidental exposure is extremely low. The treatment room is shielded to such an extent that even pregnant women may safely operate linear accelerators [1].

Leksell Gamma Knife

The Gamma Knife (also known as the Leksell Gamma Knife) is, used to treat brain tumors by administering high-intensity cobalt radiation therapy in a manner that concentrates the radiation over a small volume. The device was invented in 1967 by Lars Leksell, Ladislau Steiner, a Romanian born neurosurgeon, and Börje Larsson, a radiobiologist from Sweden's Uppsala University. The Gamma Knife (also known as the Leksell Gamma Knife) is a creation of Elekta AB, a Swedish public company, used to treat brain tumors by administering high-intensity cobalt radiation therapy in

a manner that concentrates the radiation over a small volume. The device was invented at the Karolinska Institute in Stockholm, Sweden, in 1967 by Lars Leksell, Ladislau Steiner, a Romanian born neurosurgeon, and Börje Larsson, a radiobiologist from Sweden's Uppsala University.

A Gamma Knife typically contains 201 cobalt-60 sources of approximately 30 curies (1.1 TBq), each placed in a circular array in a heavily shielded assembly. The device aims gamma radiation through a target point in the patient's brain.

The patient wears a specialized helmet that is surgically fixed to the skull, so that the brain tumor remains stationary at the target point of the gamma rays.

An ablative dose of radiation is thereby sent through the tumor in one treatment session, while surrounding brain tissues are relatively spared.

Gamma Knife therapy, like all radiosurgery, uses doses of radiation to kill tumor cells and shrink tumors, delivered precisely to avoid damaging healthy brain tissue. Gamma Knife radiosurgery is able to accurately focus many beams of gamma radiation to converge on one or more tumors. Each individual beam is of relatively low intensity, so the radiation has little effect on intervening brain tissue and is concentrated only at the tumor itself.

Gamma Knife radiosurgery has proven effective for patients with benign and malignant brain tumors up to 4 centimeters in size, vascular malformations such as an Arteriovenous Malformation (**AVM**), pain or other functional problems. For treatment of trigeminal neuralgia, the procedure may be used repeatedly on patients.

The risks of Gamma Knife radiosurgery treatment are very low and complications are related to the condition being treated.

These systems differ from the Gamma Knife in a variety of ways. The Gamma Knife produces gamma rays from the decay of Co^{60} of an average energy of 1.25 MeV [8,9].

Linear Accelerator

Linear accelerator - LINAC produces X-rays from the impact of accelerated electrons striking a high target (usually tungsten). A LINAC therefore can generate any number of energy X-rays, though usually 6 MeV photons are used. On a LINAC, the gantry moves in space to change the delivery angle.

System use a stereotactic frame to restrict the patient's movement, although on the Novalis Shaped Beam Radiosurgery system and the Novalis Tx Radiosurgery platform, Brainlab pioneered a frameless, non-invasive technique with X-ray imaging that has proven to be both comfortable for the patient and accurate. The Trilogy from Varian, or CyberKnife from Accuray, can also be used with non-invasive immobilization devices coupled with real-time imaging to detect any patient motion during a treatment.

Linear accelerators emit high energy X-rays, usually referred to as “X-ray therapy” or “photon therapy.” The term “gamma ray” is usually reserved for photons that are emitted from a radioisotope such as Co^{60} . Such radiation is not substantially different from that emitted by high voltage accelerators. In linear accelerator therapy, the emission head (called “gantry”) is mechanically rotating around the patient, in a full or partial circle. The table where the patient is lying, the ‘couch’, can also be moved in small linear or angular steps. The combination of the movements of the gantry and of the couch makes possible the computerized planning of the volume of tissue that is going to be irradiated. Devices with energy of 6 MeV are the most suitable for the treatment of the brain, due to the depth of the target. In addition, the diameter of the energy beam leaving the emission head can be adjusted to the size of the lesion by means of interchangeable collimators (an orifice with different diameters, varying from 5 to 40 mm, in steps of 5 mm). There are also multileaf collimators, which consist of a number of metal leaflets that can be moved dynamically during treatment in order to shape the radiation beam to conform to the mass to be ablated. Latest generation LINACs are capable of achieving extremely narrow beam geometries, such as 0.15 to 0.3 mm. Therefore, they can be used for several kinds of surgeries which either to have been carried out by open or endoscopic surgery, such as for trigeminal neuralgia, etc.

A LINAC produces X-rays from the impact of accelerated electrons striking a high z target (usually tungsten). A LINAC therefore can generate any number of energy X-rays, though usually 6 MeV photons are used (Figure 1).

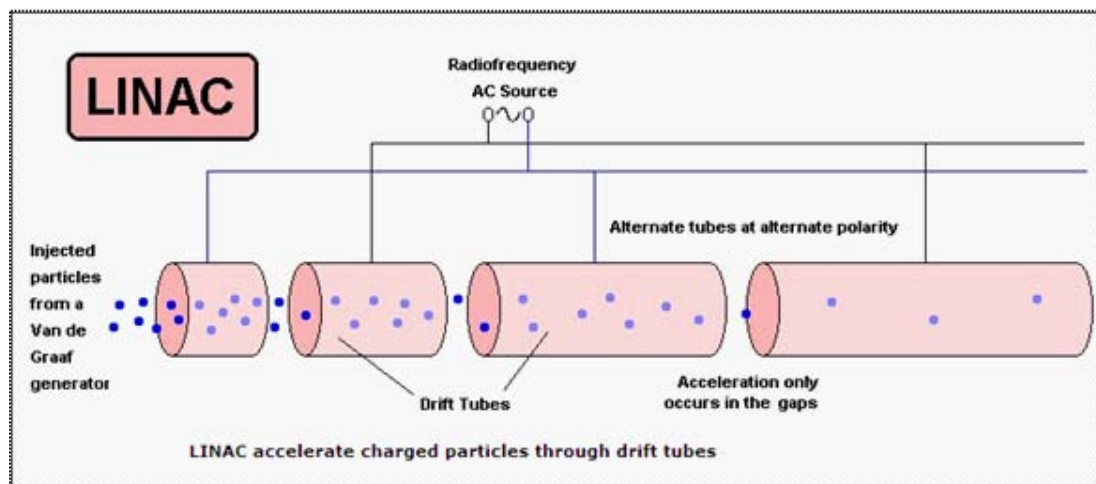


Figure 1: Schema of Linear accelerator.

The Gamma Knife has over ~200 sources arrayed in the helmet to deliver a variety of treatment angles. On a LINAC, the gantry moves in space to change the delivery angle. Both can move the patient in space to also change the delivery point. Both systems use a stereotactic frame to restrict the patient’s movement, although on the Novalis Shaped Beam Radiosurgery system and the Novalis Tx Radiosurgery platform, Brainlab pioneered a frameless, non-invasive technique with

X-ray imaging that has proven to be both comfortable for the patient and accurate. The Trilogy from Varian, or CyberKnife from Accuray, can also be used with non-invasive immobilization devices coupled with real-time imaging to detect any patient motion during a treatment (Figure 2).

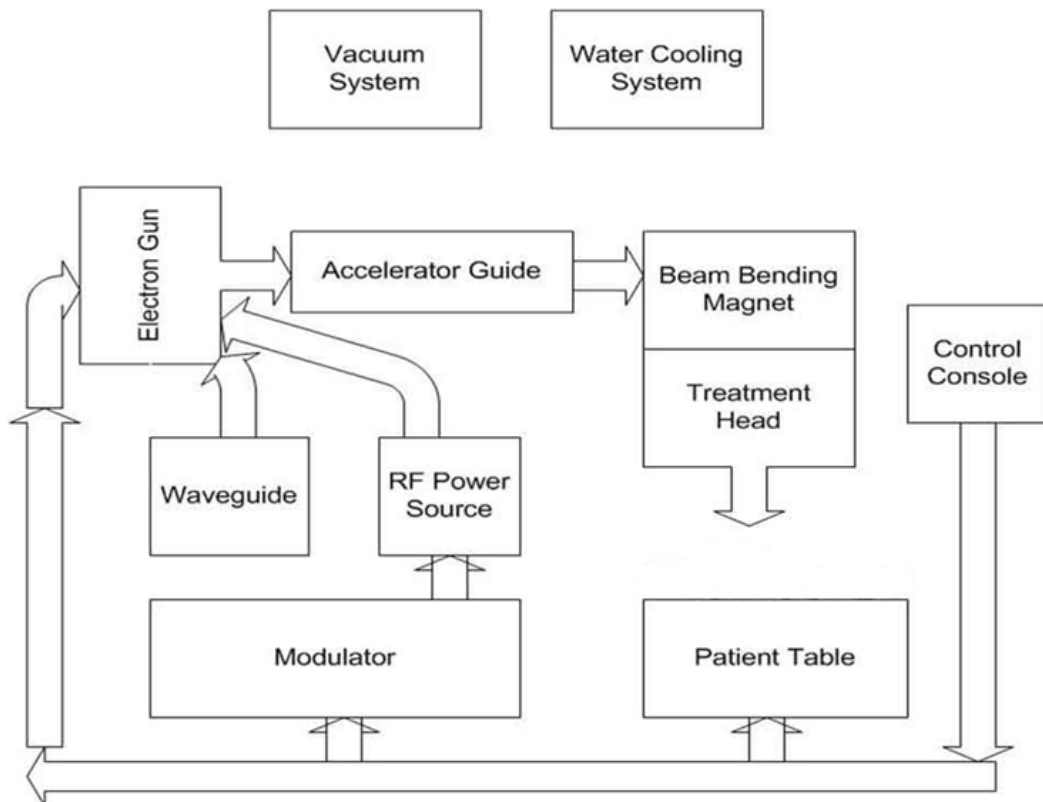


Figure 2: Structural schema of Linear accelerator.

Linear accelerators emit high energy X-rays, usually referred to as “X-ray therapy” or “photon therapy.” The term “gamma ray” is usually reserved for photons that are emitted from a radioisotope such as Co^{60} . Such radiation is not substantially different from that emitted by high voltage accelerators. In linear accelerator therapy, the emission head (called “gantry”) is mechanically rotated around the patient, in a full or partial circle. The table where the patient is lying, the ‘couch’, can also be moved in small linear or angular steps.

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Figure 3: Interchangeable collimators (an orifice with different diameters, varying from 5 to 40 mm, in steps of 5 mm).

There are also multi-leaf collimators, which consist of a number of metal leaflets that can be moved dynamically during treatment in order to shape the radiation beam to conform to the mass to be ablated.

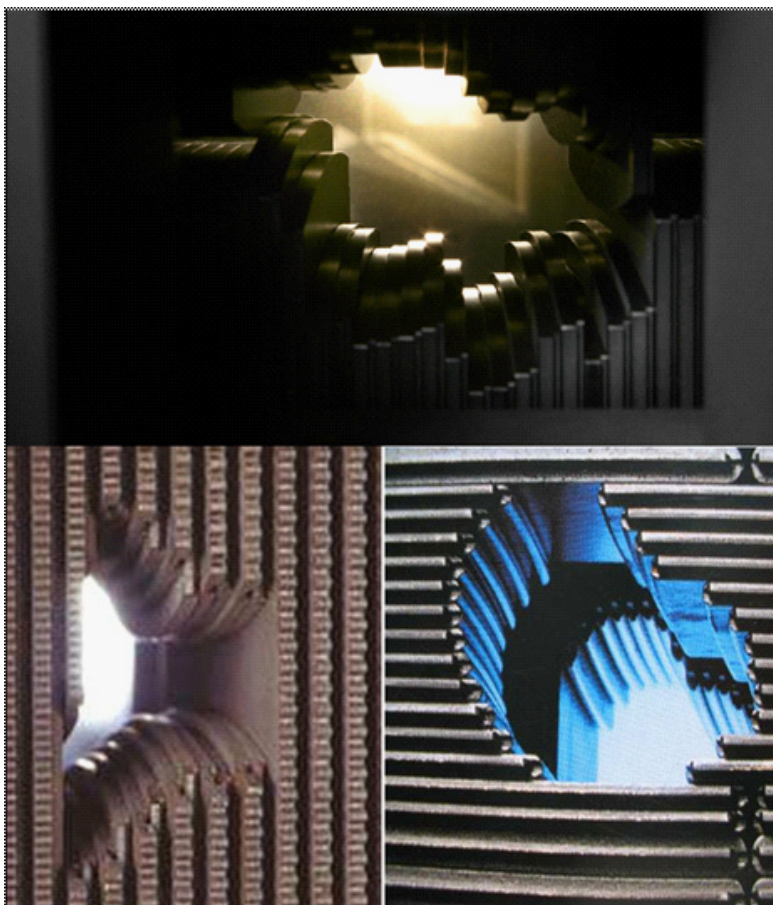


Figure 4: Multi-leaf collimators.

During conventional radiation therapy treatment, radiation beams of varying angles and intensities are directed at a target in a patient. Normal tissue and organs located in the path of the radiation beams must be taken into account for safety reasons, thereby limiting the dose that can be delivered to the target. Many techniques are known for shaping the radiation beams so that the radiation is concentrated at the target and is minimized or eliminated at the normal tissues. One of the techniques is conformal radiation therapy wherein the beam aperture varies from angle to angle via a multi-leaf collimator which employs a multiplicity of radiation blockers, called leaves. Each individual leaf in a multi-leaf collimator can be positioned independently, allowing the user to create an infinite amount of irregularly shaped fields. The radiation beams are directed between the ends of opposing arrays of the radiation blocking collimator leaves, thereby shaping the beam to closely match the shape of the desired treatment area, while shielding the normal tissue and organs (Figure 4).

Latest generation LINACs are capable of achieving extremely narrow beam geometries, such as 0.15 to 0.3 mm (Figure 5) [1,10-13].



Figure 5: LINAC with portal verify system.

The Cyber Knife

A type of linear accelerator therapy which uses a small accelerator mounted on a moving arm to deliver X-rays to a very small area, is called Cyberknife therapy. Several generations of the frameless robotic Cyberknife system have been developed since its initial inception in 1990. It was invented by John R. Adler, a Stanford University Professor of Neurosurgery and Radiation Oncology and Russell and Peter Schonberg and is sold by the Accuray company, located in Sunnyvale, California. Many such CyberKnife systems are available world- wide, and more recently it has been introduced in countries like India at leading cancer care hospitals like Apollo Specialty hospitals and HCG Bangalore Institute of Oncology.

It is a frameless robotic radiosurgery system used for treating benign tumors, malignant tumors and other medical conditions. The CyberKnife system is a method of delivering radiotherapy, with the intention of targeting treatment more accurately than standard radiotherapy. The two main elements of the CyberKnife are the radiation produced from a small linear particle accelerator and a robotic arm which allows the energy to be directed at any part of the body from any direction (Figure 6).

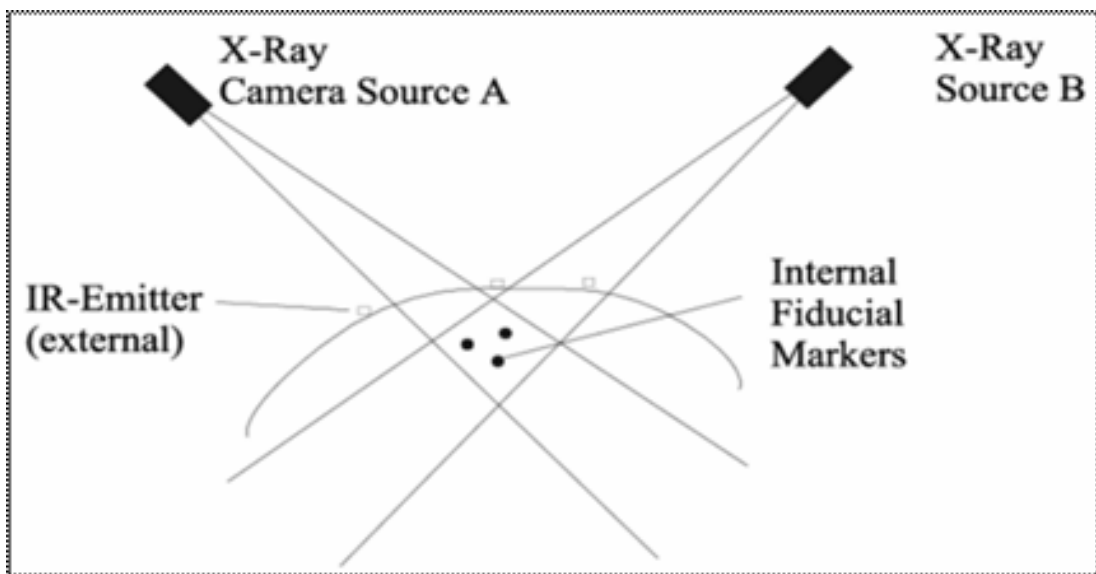


Figure 6: CyberKnife schema (X-ray images are taken every ten seconds and synchronized by timestamp with real-time infrared images. A motion pattern specific to the patient is then developed and then used to guide the Cyberknife during radiation beam activation).

Several generations of the CyberKnife system have been developed since its initial inception in 1990. There are two major features of the CyberKnife system that are different from other stereotactic therapy methods. The first is that the radiation source is mounted on a general purpose industrial robot. Mounted on the Robot is a compact X-band LINAC that produces 6MV X-ray radiation. The radiation is collimated using fixed tungsten collimators which produce circular radiation fields. Variable-aperture collimator uses two offset banks of six prismatic tungsten segments to form a blurred regular dodecagon field of variable size which eliminates the need for changing the fixed collimators. Mounting the radiation source on the robot allows near-complete freedom to position the source within a space about the patient. The robotic mounting allows very fast repositioning of the source, which enables the system to deliver radiation from many different directions without the need to move both the patient and source as required by current gantry configurations. The CyberKnife system uses an image guidance system. X-ray imaging cameras are located on supports around the patient allowing instantaneous. X-ray images to be obtained.

The original method is called 6D or skull based tracking. The X-ray camera images are compared to a library of computer generated images of the patient anatomy. Digitally reconstructed radiographs and a computer algorithm determine what motion corrections have to be given to the robot because of patient movement. This imaging system allows the CyberKnife to deliver radiation with an accuracy of 0.5 mm without using mechanical clamps attached to the patient's skull.

The use of the image-guided technique is referred to as frameless stereotactic radiosurgery. This method is referred to as 6D because corrections are made for the 3 translational motions (X, Y and Z) and three rotational motions. It should be noted that it is necessary to use some anatomical or artificial feature to orient the robot to deliver X-ray radiation, since the tumor is never sufficiently well defined on the X-ray camera images. Small metal markers (fiducials) made out of gold for bio-compatibility and high density to give good contrast on X-ray images are surgically implanted in the patient. This is carried out by an interventional radiologist, or neurosurgeon. Fiducials are known however to migrate and this can limit the accuracy. The final technology of image guidance that the CyberKnife system can use is called the synchrony method, method uses a combination of surgically placed internal fiducials and light emitting optical fibers mounted on the patient skin. A new robotic six degree of freedom patient treatment couch has been added to the CyberKnife.

In conventional frame-based radiosurgery, the accuracy of treatment delivery is determined solely by connecting a rigid frame to the patient which is anchored to the patient's skull with invasive aluminum or titanium screws. Once the frame is connected, the relative position of the patient anatomy must be determined by making a CT or MRI scan. After the CT or MRI scan has been made, a radiation oncologist must plan the delivery of the radiation using a dedicated computer program. 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. Unlike whole brain radiotherapy, which must be administered daily over several weeks, radiosurgery treatment can usually be completed in 1-5 treatment sessions. Radiosurgery can be used alone to treat brain metastases, or in conjunction with surgery or whole brain radiotherapy. During the treatment the patient need only be positioned on a treatment table and the predetermined plan delivered. While a patient is being treated, another clinician can be considering treatment options and plans, and another can be conducting CT scans. Fractionation can be beneficial from a therapeutic point of view. Tumor cells typically have poor repair mechanisms compared to healthy tissue, so by dividing the radiation dose into fractions the healthy tissue has time to repair itself between treatments. This can allow a larger dose to be delivered to the tumor compared to a single treatment [1,14,15].

Proton Therapy

The first suggestion that energetic protons could be an effective treatment method was made by Robert R. Wilson in a paper published in 1946 while he was involved in the design of the Harvard Cyclotron Laboratory. The first treatments were performed with particle accelerators built for physics research, notably Berkeley Radiation Laboratory in 1954 and at Uppsala in Sweden in 1957. From 1954 through December 2013, more than 120 000 patients across the world have been treated with particle therapy, including more than 13 000 (10.8 %) with carbon ions and more than 105 000 (87.5 %) with protons. More than 30% of those patients have been

treated for ocular melanomas. Global acceptance of particle therapy is growing, with the most rapid increase in facilities occurring in Japan and the United States. Today, about 10 new facilities are in the phase of technical commissioning, clinical commissioning, or both, and 5 or 6 of them should be ready to treat patients before the end of 2014.

Radiation from a source outside the body is focused on the tumor. For melanoma the use of this type of therapy is generally limited to newer methods that focus narrow beams directly to the tumor. Conformal proton beam radiation therapy. This procedure focuses proton beams on the tumor. Protons are positive parts of atoms that cause little damage to tissues they pass through and release their energy after traveling a certain distance. It means that proton beam radiation may be able to deliver more energy directly to the tumor and is a safer type of therapy. The treatment is not painful. The machines producing protons are expensive.

Proton therapy is a type of external beam radiotherapy using ionizing radiation. During treatment, a particle accelerator is used to target the tumor with a beam of protons. These charged particles damage the DNA of cells, ultimately causing their death or interfering with their ability to proliferate. Cancerous cells are particularly vulnerable to attacks on DNA because of their high rate of division and their reduced abilities to repair DNA damage. Proton therapy is a type of particle therapy which uses a beam of protons to irradiate diseased tissue, most often in the treatment of tumor. The chief advantage of proton therapy is the ability to more precisely localize the radiation dosage when compared with other types of external beam radiotherapy. Historically the cost of proton therapy has been an issue; however, the newer, more compact proton beam sources can be four to five times cheaper and offer even more accurate three-dimensional targeting. Due to their relatively large mass, protons have little lateral side scatter in the tissue; the beam does not broaden much, stays focused on the tumor shape and delivers only low-dose side-effects to surrounding tissue. All protons of a given energy have a certain range; very few protons penetrate beyond that distance. Furthermore, the dose delivered to tissue is maximal just over the last few millimeters of the particle's range; this maximum is called the Bragg peak.

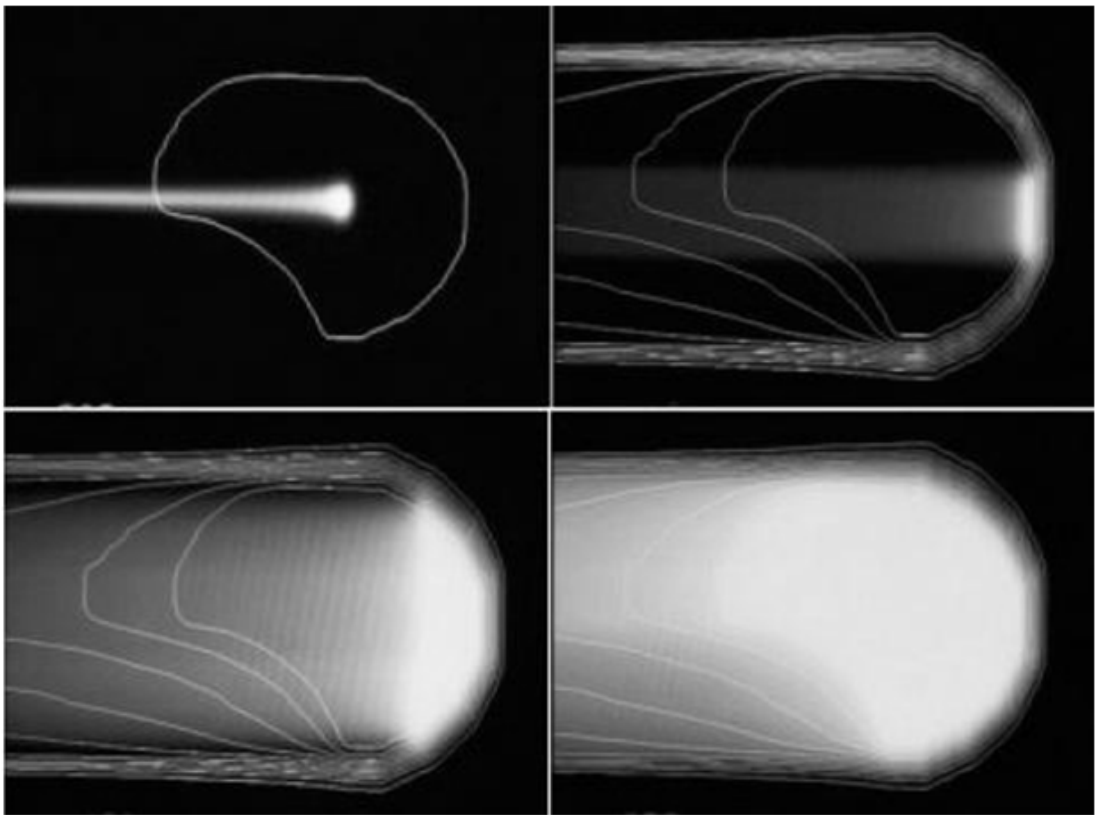


Figure 7: Bragg peak.

The Bragg peak is a pronounced peak on the Bragg curve which plots the energy loss of ionizing radiation during its travel through matter. For protons, α -rays, and other ion rays, the peak occurs immediately before the particles come to rest. This is called Bragg peak, for William Henry Bragg who discovered it in 1903.

When a fast charged particle moves through matter, it ionizes atoms of the material and deposits a dose along its path. A peak occurs because the interaction cross section increases as the charged particle's energy decreases. In the upper figure (Figure 7), it is the peak for alpha particles of 5.49 MeV moving through air. In the lower figure, it is the narrow peak of the "native" proton beam curve which is produced by a particle accelerator of 250 MeV. The figure also shows the absorption of a beam of energetic photons (X-rays) which is entirely different in nature; the curve is mainly exponential. The phenomenon is exploited in particle therapy of tumor, to concentrate the effect of light ion beams on the tumor being treated while minimizing the effect on the surrounding healthy tissue. The curve in the figure ("modified proton beam") shows how the originally mono-energetic proton beam with the sharp peak is widened by increasing the range of energies, so that a larger tumor volume can be treated. This can be achieved by using variable thickness attenuators like spinning wedges.

To treat tumors at greater depths, the proton accelerator must produce a beam with higher energy, typically given in eV or electron volts. Tumors closer to the surface of the body are treated using protons with lower energy. The accelerators used for proton therapy typically produce protons with energies in the range of 70 to 250 MeV (mega electron Volts: million electron Volts). By adjusting the energy of the protons during application of treatment, the cell damage due to the proton beam is maximized within the tumor itself. Tissues closer to the surface of the body than the tumor receive reduced radiation, and therefore reduced damage. Tissues deeper within the body receive very few protons so that the dosage becomes immeasurably small.

In most treatments, protons of different energies with Bragg peaks at different depths are applied to treat the entire tumor. These Bragg peaks are shown as thin blue lines in the figure. The total radiation dosage of the protons is called the Spread Out Bragg Peak (**SOBP**), shown as a heavy dashed blue line in figure to the right. It is important to understand that, while tissues behind or deeper than the tumor receive no radiation from proton therapy, the tissue in front of or shallower than the tumor receive radiation dosage based on the SOBP.

In a typical treatment plan for proton therapy, the Spread Out Bragg Peak (**SOBP**, dashed blue line), is the therapeutic radiation distribution. The SOBP is the sum of several individual Bragg peaks (thin blue lines) at staggered depths. The depth-dose plot of an X-ray beam (red line) is provided for comparison. The pink area represents the additional dose delivered by X-ray radiotherapy which can be the source of damage to normal tissues and of secondary tumors, especially of the skin.

Particle Beam Radiation Therapies for Cancer which protons are used can be separated into two broad categories. The first are those for disease sites that favor the delivery of higher doses of irradiation, i.e. dose escalation. In some instances dose escalation has been shown to achieve a higher probability of “cure” (i.e. local control) than conventional radiotherapy. These include (but are not limited to) uveal melanoma (ocular tumors), skull base and paraspinal tumors (chondrosarcoma and chordoma) and unresectable sarcomas. In all these cases proton therapy achieves significant improvements in the probability of local control over conventional radiotherapy. In treatment of ocular tumors, proton therapy also has high rates of maintaining the natural eye.

The second broad classes are those treatments where the increased precision of proton therapy is used to reduce unwanted side effects, by limiting the dose to normal tissue. In these cases the tumor dose is the same as that used in conventional therapy, and thus there is no expectation of an increased probability of curing the disease. Instead, the emphasis is on the reduction of the integral dose to normal tissue, and thus a reduction of unwanted effects.

Two prominent examples are pediatric neoplasm (such as medulloblastoma) and prostate cancer. In the case of pediatric treatments there is convincing clinical data showing the advantage of sparing developing organs by using protons, and the resulting reduction of long term damage

to the surviving child. Children with cancer are major beneficiaries, because the proton beams are able to target tumors with great precision, sparing neighboring tissue. That's especially valuable for children because their bodies are still growing. Traditional radiation often stunts growth in children with cancer.

The case of prostate cancer the issue is not so clear. Some published studies found a reduction in long term rectal and genito-urinary damage when treating with protons rather than photons (also known as X-ray or gamma ray therapy).

Proton therapy for ocular (eye) tumors is a special case since this treatment requires only comparatively low energy protons (about 70 MeV). Owing to this low energy requirement, some particle therapy centers only treat ocular tumors. Proton, or more generally, hadron therapy of tissue close to the eye affords sophisticated methods to assess the alignment of the eye that can vary significantly from other patient position verification approaches in image guided particle therapy.

In proton therapy for ocular (eye) tumors position verification and correction have to ensure that sensitive tissue like the optic nerve is spared from the radiation in order to preserve the patient's vision [1].

Brachytherapy (Episcleral Plaque Therapy)

Isotope considerations I^{125} : standard, low-energized, was mandated in COMS trials Pd^{103} lower energy than I^{125} , with faster dose fall-off. Minimal sclera radiation dose of 300-400 Gy and a minimal apex dose of 80-100 Gy to the tumor apex are reasonable for cure (Lommatsch, 1978). Parameters can be met if tumor apex ≤ 5 mm, good choice for small melanomas. Co^{60} : high-energy gamma, which may result large dose to unaffected ocular structures, and health care providers Ir^{192} same as Co^{60} plaque brachytherapy is typically used alone. In certain cases physician may want to add laser photocoagulation. The radiation sources used for brachytherapy come in the form of small "rice-sized" radioactive seeds. These seeds are attached within a gold or steel bowl called a plaque. The dose of radiation delivered to the tumor is determined by the type, number and strength of the seeds used and length of time of the implant. The dose will also depend on the size of the tumor and its location. It is necessary to compare between various types of available eye plaques (e.g. Ru^{106} , I^{125} and Pd^{103}) before surgery. Though both can destroy the tumor, the plaque that delivers less radiation to macula, optic nerve and fovea will offer the best chance of keeping the best visual acuity (over time).

During the procedure, the eye tumor specialists will attach the plaque to the wall of the eye, covering the intraocular tumor. Placement of the plaque is performed in the operating room. A comprehensive review of radiation therapy for choroidal melanoma showed that many forms or sources of radiation have been used to treat intraocular tumors. It is reasonable to assume that by given a large enough dose all of these radiation techniques can destroy intraocular tumors.

They differ in the distribution of ocular and orbital radiation dose, and their resulting radiation side effects. For example, proton radiation will affect those tissues through which beams travel the tumor (typically the eyelashes, eyelid, conjunctiva, cornea, lens, iris and ciliary body), whereas plaque radiation travels through the wall of the eye (sclera and cornea) in order to reach an intraocular tumor. Finger's review showed that external beam therapy resulted in more reported anterior complications than plaque therapy in choroidal melanoma.

These findings, and our desire to improve radiation safety, have driven an evolution in treatment techniques. Finger currently recommends the use of Pd^{103} for plaque radiation therapy of most choroidal melanomas. Studies have shown that low-energy I^{125} plaques have largely replaced Co^{60} and Ru^{106} for plaque radiation therapy (Figure 8). Nowadays this therapy places small pellets of radioactive material directly into or very close to the tumor. This has become the most commonly used radiation treatment for majority of eye melanomas. The pellets of radioactive material are attached to a small carrier (a very small bottle cap), which is placed on the outside of the eyeball with tiny stitches to keep it in place. The carrier is made of gold or lead to shield nearby tissues from the radiation. The radiation from the pellets travels a very short distance, so most of it will be focused only on the tumor. An operation is needed to put the plaque (radioactive element and carrier) in place. This surgery usually takes one or two hours. Plaque therapy typically involves attaching a dish-shaped radiation source beneath the tumor and leaving it there for 5 - 7 days. Compared with proton-beam, the front of the eye usually receives much less radiation with plaque radiation therapy, but parts of the posterior part of the eye receive more. This is why anterior "front of the eye" complications (eye lash loss, severe dry eye, neovascular radiation glaucoma) are unusually seen after low-energy (I^{125} , Pd^{103}) ophthalmic plaque radiation therapy. However, laser treatment and anti-VEGF intravitreal therapies can be used to reduce the chance of radiation associated vision loss (after plaque therapy). Tumors that touch the optic nerve are more difficult to treat with ophthalmic plaque radiation therapy. Special notched plaques can be used in this situation. Finger has recently developed specialized "Finger's slotted plaques" for treatment of tumors touch or encircling the optic nerve. Due to the advent of super-sized 24 mm (for extra-large tumors) and Finger's slotted eye plaques (for tumors around the optic nerve), fewer than 8 % of patients require enucleation as treatment for choroidal melanoma (at The New York Eye Cancer Center). Clearly, ophthalmic plaque radiation therapy is the most widely available and most commonly used eye and vision-sparing treatment for choroidal melanoma. Radiation affects cells by creating free-radicals (primarily hydroxyl $\text{OH}\cdot$) in humans which can directly destroy cells by breaking cellular DNA. This means that there are some immediate tumor killing effects and other effects which will not show up until the cell tries to divide (using its broken DNA). Cells that will die when they try to divide are considered sterile and incapable of metastasis. Radiation damages both the tumorous as well as normal tissues. This is one reason why tumors tend to shrink slowly, and why some radiation complications appear years after treatment. Complications can occur after radiation therapy for intraocular and orbital

tumors. The incidence of these complications is related to the dose given, how fast it is given (dose-rate), the age of the patient, other synchronous diseases, and the individuals tolerance for radiation therapy. In general, larger tumors require more radiation to kill their cells as do some tumors which are less radiation sensitive. Large differences exist between plaque therapies which typically deliver radiation constantly for 5-7 days, as compared to external beam therapy, which typically delivers 5 daily doses of 1200-1500 cGy in 5 minutes (each). Both require surgery [1,16].



Figure 8: Velhagen's episcleral Ru¹⁰⁶ applicators.

Stereotactic Radiosurgery

This treatment delivers a large, precise radiation dose applied to the tumor area in only one session. The radiation may be delivered in one or two ways. Radiation beams are focused at the tumor from hundreds of different angles for a short period of time. The machine used to deliver this type of radiation is known as a Gamma Knife.

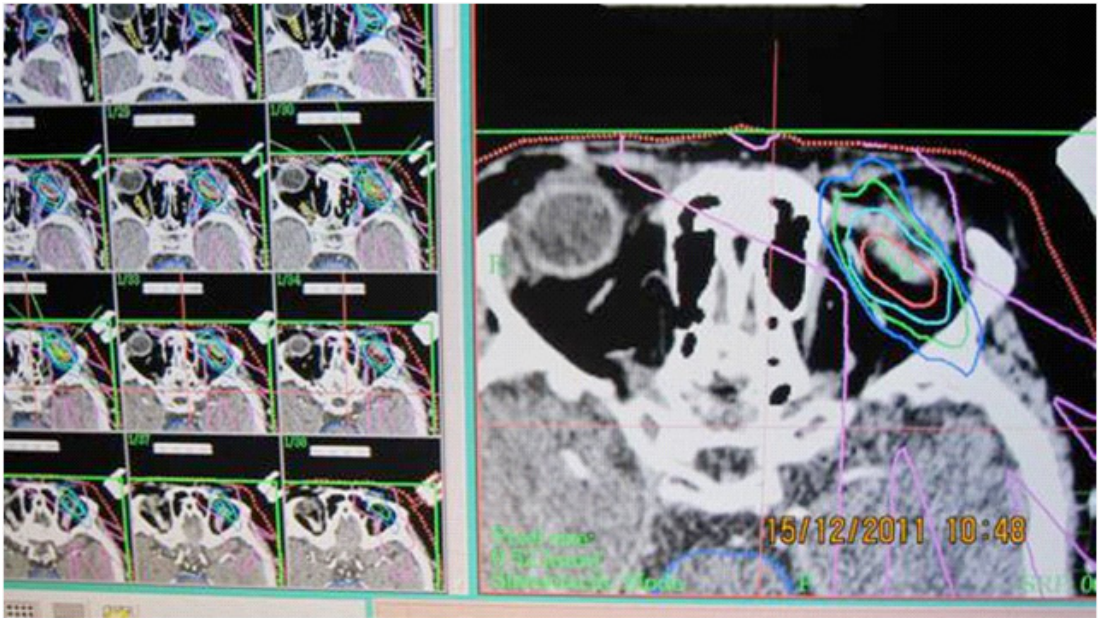


Figure 9: Stereotactic radiosurgical planning scheme of patient with large posterior malignant uveal melanoma.

LINAC-based stereotactic radiosurgery of posterior uveal melanoma is a conservative method of treating uveal melanoma. The LINAC-based SRS treatment is a method to treat middle stage posterior uveal melanoma while preserving the eyeball (Figure 9,10) [17-21].

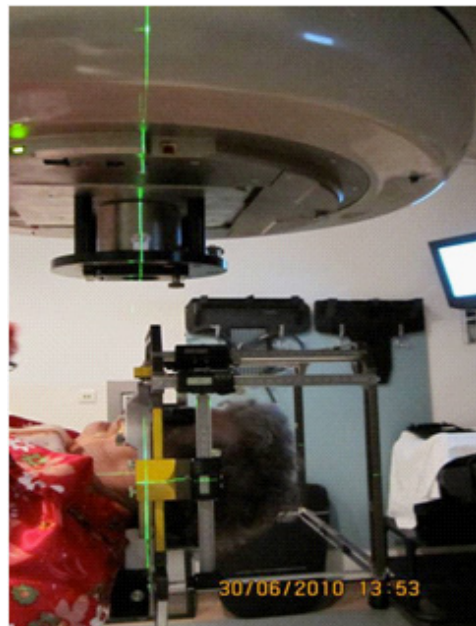


Figure 10: Position of the patient by stereotactic radiosurgery at linear accelerator.

SURGERY

Surgery is effective in the treatment of some intraocular melanomas. The type of surgery depends on the location and size of the tumor and includes:

Iridectomy

Removal of part of the iris. It's an option for very small iris melanomas.

Iridotrabeculectomy

Removal of part of the iris, plus a small piece of the outer part of the eyeball.

Iridocyclectomy

Removal of a portion of the iris and the ciliary body (Olah, 1983).

Resection

Resection (removal) of a melanoma of the ciliary body or choroid. This can be used for small melanomas.

Enucleation

Removal of the entire eyeball. This is used in more advanced melanomas (T4 or large T3 tumors), but it may also be done in some smaller melanomas if other treatment options would destroy useful vision in the eye anyway (Figure 11,12).

Exenteration of the orbit - orbital exenteration implies the removal of all the orbital contents including the periorbita and eyelids, it is necessary in stage T4, when the tumor penetrates throughout the sclera and infiltrates the orbital tissue.



Figure 11: Enucleated eyeball with uveal melanoma (arrow) infiltrating the anterior chamber.



Figure 12: Patient with large uveal melanoma after enucleation, conjunctival sac before applying an individual prosthesis, individual prosthesis and patient with applied individual prosthesis.

Exenteration of the orbit is the most radical option, the removal of all of the eye, the associated muscle structures, and occasionally part of the orbital bones. Exenteration is used for advanced stages, when other methods of tumor treatment have failed (Figure 13) [1,22].



Figure 13: Patient after exenteration of the orbit due to large melanoma infiltrating the orbit with an epithesis.

OTHER TREATMENT MODALITIES

Laser Therapy

Lasers are highly focused beams of light that are able to destroy tissue and sometimes can be used to treat intraocular melanoma. On the contrary, this type of therapy cannot treat intraocular lymphoma. Transpupillary Thermotherapy (**TTT**) is the most common type of laser treatment for intraocular melanoma. It uses infrared light to heat the tumor causing its lethal damage. TTT may be useful for treating small choroidal melanomas. It may be used as an additional treatment after brachytherapy. Usually one to three therapeutic sessions is/are necessary to kill the tumor. Laser photocoagulation is a procedure that uses laser light to destroy blood vessels that supply nutrients to the tumor, causing necrosis of the tumor cells. This treatment uses a highly focused, high-energy light beam. It can be effective for small melanomas, but it is more often used to cope with side effects of radiation. Several laser treatments are usually given 6 or 8 weeks apart to treat a tumor. Photocoagulation therapy is a method of treating detachments (tears) of the retina with an argon laser. The high-intensity beam of light from the laser is converted into heat, which forces protein molecules in the affected tissue to condense and seal the tear. The purpose of photocoagulation therapy is to reattach a torn or detached portion of the retina and/or prevent further growth of abnormal blood vessels in the retina that can cause a detachment. The main concern with laser therapy is that it may damage parts of the eye that further result in loss of vision. The risk depends on the size and location of the tumor [1].

Thermotherapy and Chemotherapy

Thermotherapy is the use of heat in order to destroy tumor cells and may be given using:

- Microwaves
- Laser beam aimed through the dilated pupil or onto the outside of the eyeball
- Ultrasound
- Infrared radiation.

Chemotherapy is the use of anti-tumor drugs that are administered into a vein or are taken by mouth. These drugs enter the bloodstream and reach throughout the body. Chemotherapy is used rarely for intraocular melanoma than other types of cancers. Some chemotherapeutic drugs may be injected directly into the eye. This concentrates the chemotherapy at the site of the tumor, allowing higher doses to be given without causing severe side effects in other parts of the body. Melanoma usually does not respond positively to chemotherapy. Chemotherapy is used only when the tumor spreads; the treatment scheme is the same as for melanoma of the skin [1].

Anti-VEGF Treatment in Uveal Melanoma

Anti Vascular Endothelial Growth Factor Medications (**Anti-VEGFs**) are substances that stop blood vessels from forming or growing. Anti-VEGFs is a category of drugs, which work by targeting a protein that is necessary for new blood vessels formation. Blocking VEGF can reduce the growth of new blood vessels, slow. Their leakage and slow down vision loss. There are currently three drugs that have been used in the treatment of wet macular degeneration: pegaptanib sodium injection (Macugen), ranibizumab injection (Lucentis) and bevacizumab (Avastin) [1].

FOLLOW-UP CARE

It is very important for the patient to keep all follow-up appointments. During these visits, doctors ask about symptoms, do physical exams, and even ask for blood tests or imaging tests such as MRI or CT scans. Follow-up is needed to check for tumor recurrence or spread, as well as possible side effects of certain treatments.

Almost any cancer treatment can have side effects. Some may last for a few weeks to several months and others may last for the rest of the patient's life. The time between visits may be extended if there are no problems. Physical exams are done to look for tumor recurrence or side effects of treatment as early as possible. Imaging tests such as chest X-rays, ultrasound, CT or MRI scans may be done to watch for recurrence or metastasis. Most recurrences can be treated more effectively if they are found early. If cancer does reoccur at some point, further treatment will depend on the location of the tumor, what treatments one has had before, and one's health.

Ophthalmologists check the treated eye for complications and may recommend medicines or operations to help control side effects and help to keep the vision as clear as possible. Patient is monitored in 2 weeks, later 6 weeks and 3 months interval (visual acuity, intraocular pressure, slit lamp examination, fundusphoto, ultrasound- Bscan, OCT, perimetry). In 3 months interval patient is send to MRI control.

Follow-up exams and tests are also important for people who have had an eye removed, because melanomas can still sometimes reoccur in the area around the eye or in distant parts of the body.

Patients are recommended regularly in six month interval to their oncologist to a liver ultrasound, abdominal ultrasound, liver's function test; once per year chest X-ray to confirm or exclude the presence of metastases. In 3 months interval patient is send to MRI control. In individual cases they are recommended to brain CT or PET (positron emission tomography).

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