Cancer may not be as common in horses as it is in our small animal population but it does occur. In small animal oncology, cancer therapy has been increasingly in demand and newer and better therapies are becoming more available. Radiation therapy is often used to control tumors locally and the radiation itself is being given in ever more sophisticated ways. The shear size of horses can make therapies such as radiation seem impossible. Radiation is a valuable tool for the treatment of cancer however, and should not be over looked for the treatment of equine patients.

I. Biology of radiation

Radiation therapy works primarily by depositing energy on or near the DNA of cells. Because the DNA is damaged, cells die when they try to divide. Although radiation seems like magic, it is never as selective as we would like. Normal and cancer cells are killed, and only a constant proportion of cells are actually killed with each dose. If a single large dose of radiation is given, it may be possible to kill a tumor but, normal tissues would be severely damaged as well. Increased survival of normal tissue is achieved if radiation is given over a prolonged time, or it is broken into many small doses of therapy. Factors affecting the cells sensitivity to radiation therapy which can be some what exploited by prolonging therapy are their ability to repair, and repopulate, where they are in their cell cycle, and the presence of oxygen. Theoretically, these parameters can change over time, or after a dose of radiation is given, and a portion of the cells are destroyed, thus they are often referred as the 4 R’s- or Repair, Repopulation,
Redistribution, and Re-oxygenation. These 4-R’s form the basis for most fractionated radiation protocols, which involve delivery of several small fractions of the total dose of radiation - instead of one large dose. The goal in spacing out therapy is to kill the maximum number of tumor cells and yet allow time for repair and repopulation to occur in the normal cells so that the normal cell population survives.

A total dose of radiation is chosen based on what is needed to kill the tumor, a time interval is chosen based on the tumor and the normal surrounding tissues, and the fraction size is chosen based on the tissue in the field that has the least ability to cope with large doses of radiation per fraction. These are late responding tissues, or those with the most catastrophic results when there is failure to repair, such as nervous tissue, bone, and the fibrous layers in skin. Typical fractionation schemes in small animals are 2-3 Gy fractions, daily M-F, to a total of 18-20 fractions. Variations are sometimes made to treat tumors that repopulate too quickly (e.g. feline squamous cell carcinomas) where the overall treatment time is shortened by treating twice a day. Also tumors deemed “incurable” due to size (the surgeons didn’t want to touch it) or metastatic potential (melanomas) can be treated with less aggressive, more course coarsely fractionated protocols (6-8 Gy fractions 3-5 times) because the patient is not expected to live long enough to experience the “late” side effects of radiation. Interestingly in the case of melanomas large fraction therapy is also best to treat the tumor.

When considering the tumor as a whole as a candidate for radiation therapy, other factors come in to play- the number of cells that needs to be treated and the size of the tumor, sensitivity of the tumor cells, and equally important as tumor factors- the sensitivity of the surrounding tissues to effects of radiation. Often the best plan is to
decrease the tumor size and actually increase the sensitivity of the tumor cells by removing as much as possible surgically. Generally, surgery is planned with the attempt to remove the entire tumor, or at least all that is visible. Radiation is then expected to only clean up microscopic dirty margins. For some tumor types, getting rid of whatever you can, or “debulking,” can be helpful prior to radiation while for others the debulking process can just bring problems. This is why determination of tumor type and tumor imaging can be so important prior to surgery.

The goal of radiation treatment planning is to deliver the highest possible dose to tumor, and the lowest dose to normal surrounding tissue. This may seem easy- but at times it can be quite difficult and even impossible. Surrounding tissue sensitivity is something that usually can not be changed, and at times it can be the dose limiting factor in the treatment of the tumor. Generally, doses have to be adapted to spare neurologic tissue and bone (fraction size and total dose), but eyes, the oral cavity, and other structures can also limit radiation’s ability to cure. In horses this may seem easier as tumors in the brain or spinal cord would rarely be treated, and horses in general are quite large with more tissue to deal with. Tumors do however, occur around the eye, in the sinuses near the brain, and overlying bone, so these concerns are real. Also- positioning a horse accurately to repeat a carefully designed radiation plan can be difficult.

Despite all attempts at sparing normal tissues, there are side effects to radiation therapy. These can generally be divided into early and late effects. Early effects happen within 3 months post-therapy, are expected, and will get better. Early effects involve tissues that are rapidly dividing. They include hair loss, irritation of the skin caused by the cornified outer layer of the skin being absent for a time, mucositis, and conjunctivitis.
Symptomatic therapy and patience is generally the best treatment for early side effects, and care must be taken not to damage the tissues further (animal scratching, or human scrubbing). Late effects occur months to years after radiation and will not get better. Acceptable side late effects include alopecia and hyperpigmentation of the skin, and cataract formation. Less acceptable effects would be nervous tissue atrophy or necrosis, bone necrosis, and skin fibrosis. These are serious side effects that may mean the treatment itself was done improperly. In general it would appear that horses tend to tolerate radiation very well in both the early and late phases.

II. Types of radiation

Brachytherapy – or short distance radiation therapy- involves placement of radiation very close to the tumor or most often within the tumor itself. Interstitial therapy uses small seeds of radioactive material implanted into a tumor. In many ways this is the ideal way to treat many superficial tumors as the treatment is confined to the tumor area and maximizes the ability to treat the tumor and spare the normal. Also sources generally deliver a low dose rate, but because they are left in place and exposure is constant, a relatively high total dose of radiation is delivered over a short time period. Implantation can be performed under a local anesthesia or a single anesthetic episode. Many types of interstitial seeds have been used in horses in the past with the main variable being the radioactive source and its half life. Gold 198 (T\textsubscript{1/2} -2.7 days), Radon 222 (T\textsubscript{1/2} -3.83 days), Iridium 192 (T\textsubscript{1/2} -74.2 days), Iodine 125 (T\textsubscript{1/2} -60.2 days ), and even Cesium 137 (T\textsubscript{1/2} – 30 years) and Cobalt 60 (T\textsubscript{1/2} – 5.26 years), have all been used in equine radiation therapy\textsuperscript{1-11}. Implants are left in place temporarily or permanently. Permanently placed
seeds are left in place and the dose is delivered slowly over time as the radioactive source decays. Temporary implants are meant to be left in place until the desired dose of radiation has been delivered and then removed. Seeds are surgically implanted using pre-placed nylon catheters into which the radioactive sources are inserted using long handled forceps and speed. Handling of the seeds and handling of the horses with implants are all potential times for humans to be exposed to radiation, and some states and facilities no longer allow interstitial therapy in equines. For temporary seeds the implants must also be removed, again a potential source of human exposure. An alternative is to use a “remode afterloading” device with a high activity source (Iridium 192). After placement of catheters a single source controlled by a computer enters each catheter for prescribed distance and time allowing treatment of the entire tumor. This form of brachytherapy delivers a fairly high dose rate in a short time and the treatments must be fractionated into more than one treatment. The draw back to this is that the catheters are left in place between treatments and this can be bothersome to the horse. Also the horse needs to be anesthetized for each treatment.

Although brachytherapy is highly successful it is not without complications and hazards to both the patient and the humans involved in the care of the horse. Dose of radiation is determined by time of decay of the source or time left in place in the case of temporary implants, also- proximity of one source to another. With precise planning the dose can be evenly distributed and hot spots can be avoided. Treatment around eyes will cause radiation of the eye itself because the eye cannot be shielded while the treatment is ongoing. Horses are to remain isolated- but there will still be human contact. Also it can
not be guaranteed a horse with seeds in place will not rub at the tumor and dislodge seeds implanted temporarily.

**Plesiotherapy** - close to, or very short distance radiation therapy - is usually used to describe treatment with Strontium 90. This beta emitting source is hand held and can treat an area of about 5-8 mm. Because it is beta radiation the maximum penetration into tissue is only 3 mm, with 60% of the dose being delivered within the first 1 mm. A high surface dose of radiation (20-25 Gy) can be given because the dose is extremely localized. Time needed for a single treatment site is around 10-15 minutes, and multiple contiguous sites can be treated to treat a larger area. Over time the sources decay, and lower radiation doses rates are delivered such that treatments require more time. Generally the horse must be fully anesthetized or heavily sedated to accomplish therapy.

**Teletherapy** - therapy at a distance - or use of an external beam of radiation to treat a tumor at any depth. At one time external beam therapy was similar to interstitial therapy in that a radioactive source was used (Cesium or Cobalt) to generate gamma rays, or a photon beam. These days most external beam radiation is delivered using a linear accelerator which, often has the capability of producing two distinct forms of radiation. Electrons are used as therapy beams and these allow for the precise treatment of superficial tumor. Electrons have the amazing feature of delivering their dose of radiation over a fairly short distance down into the tissues (1-4 cm depending on the energy of the electron beam), and then their dose falls off quite rapidly so that very little dose is delivered deeper into the tissues. Photon beams are generated when accelerated
electrons strike a target much like a diagnostic xray unit, accept in the treatment setting the energy of the product beam is much higher (at least 6 MV). These high energy photon beams are used for penetrating more deeply into tissues. The dose at the skin surface is negligible but the photon beam continues to deliver dose quite deeply into tissues. This is why when photon beams are used the dose must often be delivered from several sides, summing to a treatment dose in the center. Electron or photon beams both deliver high dose rate therapy to a localized field and surrounding tissues are treated as well. Therapy is nearly always fractionated to bring about a better tumor kill and less side effects to surrounding tissues. Linear accelerators are costly pieces of equipment and rooms with maximal shielding are required to house them. Patients must remain absolutely still to be sure the treatment is being given in the correct location as the beam is stationary and does not move with the patients. Also no one is in the room when therapy is occurring. For animal patients this necessitates anesthesia.

For equines many biases against teletherapy have long existed. The need for repeated anesthesias was often a big deterrent. Even today, facilities that can irradiate horses will often use fractionated protocols involving much fewer fractions of therapy than would be used for small animals. The facilities themselves must be built with equine treatment in mind. Small animals can be treated on a treatment couch designed for humans, and they are often anesthetized in the same room. Horses need their own treatment couches, anesthesia is induced at another location and the horse must be able to be transported into the treatment room. Any Linear accelerator itself can treat a horse, it is everything around the machine that needs modification if a facility wants to treat
horses. Because of these concerns it seems as if a bias has also built up within the equine world against considering radiation therapy as potential treatment for equine tumors.

At WSU the Linear accelerator vault was built with treatment of horses in mind. A variety of equine tumors have been treated over the past 10 years but generally that bias against multiple anesthesias has existed here as well. More recently when consider treatment of cutaneous squamous cell carcinomas (SCC), the question arose as to which was easier with a horse- hold them off food every other day for anesthesia 9-10 times over a 3-4 week period (typical coarse fractionation protocols would require this) or anesthetize them twice daily for 5 days and be done (an accelerated protocol).

Accelerated radiation protocols as stated earlier are aimed at treatment of rapidly growing tumors, such that tumors have little time to recover between treatments. Twice daily treatments have been used for treatment of feline SCC, and human SCC. Also the shortened treatment time would more closely approximate therapy delivered using interstitial radiation. Our protocol became 2 treatments daily divided by a space of 6 hours, delivered over a 7 day period because treatments were divided over a weekend (cats are generally treated in a total of 5 days). Three horses have been treated with this rapid protocol and none had problem related to anesthesia other than the largest of the 3 having slow recoveries forcing some single treatment days and a total protocol of 9 days. Two horses with SCC had complete resolution and one sarcoid resolved for roughly one year but then began to reoccur. This protocol is not ideal for every tumor or location, but it does highlight the fact that the general bias against multiple anesthesias, in close succession, in a horse, may be unfounded.
III. Treatment specifics of horses

Tumors one should consider as candidates for RT are numerous, and in small animal medicine there is little we won’t at least attempt to palliate with radiation. One of the few requirements is that the tumor has not metastasized or in general has no tendency to metastasize. In horse it is more difficult to “stage a patient”. Staging refers to all the exams that are necessary to determine whether the tumor may have spread to another location. In small animals this includes careful exam of draining lymph nodes, which also needs to be done in our equine patients. If the draining lymph nodes are too deep to palpate, ultrasound may aid in finding them. The thorax of small animals is always examined with at least thoracic radiographs and also possibly thoracic CT. This is much more problematic in equines and we are limited to the radiographs we can get. Beyond this- it is the knowledge of the tumor’s usual behavior that more or less determines whether we consider the equine patient at high risk for metastasis or not. Location of the tumor can also be important. Treatment will always be easier in the extremities and head as they are much easier to position, but other areas can be treated as well as long as the body part fits under the beam.

**Brachytherapy:** Use of interstitial implants in equines tumors has been highly successful for the treatment of sarcoids and cutaneous SCC. Early studies with Cesium or Cobalt and periocular SCC (1978) showed good results with two year tumor control rates of 68%\(^1\). Subsequent studies have shown tumor control rates at 2 years of 74-81%. Sarcoids
have been treated with slightly higher success rates between 87-100%. Important factors in determining the success of therapy include the total dose of radiation delivered and the size of the tumor. Smaller tumors will be better controlled which often necessitates a surgical debulking be performed first. Although interstitial implants are highly successful, only a few veterinary schools across the country are still allowed to implant tumors. Dislodging of the seeds into the horses stall and exposure to staff working with the horses are big reasons for this change. WSU does not currently use brachytherapy.

**Plesiotherapy:** Use of Strontium 90 for radiation therapy is also highly successful but is limited to small superficial tumors and often this is a post surgical treatment. Commonly it is tumors around the eye treated in this fashion- most likely this is because tumors in this area may be found when small enough to treat with the small probe. WSU does have a Strontium probe and we do still use it on occasion.

**Teletherapy:** External beam radiation has been used on a limited basis to treat deep seated tumors in equines. Reports have been published of treating; a mandibular ossifying fibroma where 2 years later tumor had not returned; SCC of the nasal cavity and paransal sinuses in three horses where survivals were 6, 3.5, and 2.5 years; and a recurrent ossifying fibroma in the paransal sinuses of a horse where tumor was controlled for > 6 years. Unpublished cases are likely numerous, but still at much lower numbers than what is currently being treated in small animal oncology. A variety of tumors have been treated at UC Davis including head and neck SCC, osteomas, fibromas and ameloblastomas of the oral cavity, melanomas, nasal tumors, and extremity SCC, and
other institutions including WSU. Radiation outcomes have been uniformly successful and side effects are generally minimal. And such good results have often been attained with fairly coarsely fractionated protocols meaning fewer and larger dose fractions than would be thought of as ideal for small animals or humans.

**What can we treat?** Melanomas and sarcoïds can be treated with large fraction radiation (only 3-4 doses of 6-8 Gy) quite effectively. Squamous cell carcinomas obviously respond well to a variety of protocols. Lymphosarcoma in a single location will respond exquisitely and rapidly to RT. Tumors of the sinuses can be effectively treated with far better success than periodic surgical debulking. Even brain tumors could be potentially treated in equines. The most likely candidates would be horses with pituitary tumors. Pituitary tumors under 2cm in diameter in dogs and cats are treated with a single dose of radiation, and this may be possible in horses as well.

Cost of radiation can be a deterrent but if owners can be offered a treatment that will give their horse an additional 2-10 years longer, without loss of a body part such as an eye, they would probably be willing to spend the $2,000.00-6,000.00 that it will cost to have their horse irradiated. Travel can also be a problem, but facilities willing to treat horses are scattered across the US. Perhaps the biggest limiting factor to equine radiation is the mind set of clinicians who don’t consider this as a treatment option. This, despite the good results achieved historically when radiation therapy has been used. Outcomes for horses with SCC of the eyelid and peri-ocular structures were significantly better if treated with adjuvant radiation therapy versus those who were not, with recurrence rates of
only 11.9% versus 44.1%. Radiation therapy for horses- it does have more potential than you would think!