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Principi di base nella diagnosi e nel trattamento delle neoplasie nel cavallo

Basic principles of diagnosis and management of neoplasia in horses

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Riassunto

Saranno illustrati i principi di base della diagnosi e del trattamento delle varie malattie neoplastiche comuni negli equini. La diagnosi viene spesso formulata sulla base di una supposizione intuitiva, ma talvolta questa può portare ad errori di giudizio nella terapia e nella prognosi. Il valore della biopsia è indiscutibile, ma in alcuni casi il ricorso a questa tecnica non è necessario (ad es., melanoma), mentre in altri può essere specificamente controindicato (ad es., alcune forme di sarcoide degli equini). Certi tipi di trattamento sono difficili da applicare per ragioni logistiche (ad es., radioterapia), mentre altri sono molto più facili (escissione chirurgica di piccoli melanomi focali), ma alcuni interventi comportano gravi rischi per l'operatore, il cavallo o l'ambiente (o per più di uno di questi elementi). Il recente rinnovamento dell'interesse per l'oncologia equina ha portato ad alcuni nuovi trattamenti come l'impiego del cisplatino nel carcinoma squamocellulare e nel sarcoide o l'uso della cimetidina nel trattamento di alcuni casi di melanoma. Si stanno compiendo notevoli miglioramenti nella comprensione dei processi neoplastici di tutte le specie animali e, anche se il cavallo è generalmente un modello poco adatto e le prove cliniche sono difficili da condurre (per diverse ragioni), alcuni di questi riscontri stanno offrendo migliori opportunità a lungo termine per i trattamenti oncologici. Tuttavia, restano i gravi limiti alle opzioni terapeutiche, che sono dovuti principalmente alle dimensioni ed alla natura di questa specie animale. I farmaci sono di solito costosi e vanno impiegati in quantità elevate, per cui le gravi neoplasie interne sono raramente suscettibili di terapia. Nella maggior parte dei casi, i proprietari si aspettano una diagnosi e poi una prognosi accuratamente considerata. I veterinari devono cercare di evitare di fare affermazioni avventate sui singoli casi senza prima valutare il cavallo nel suo complesso e la capacità/volontà del proprietario di intraprendere il trattamento proposto. Non c'è nulla di peggio di un conto elevato ed un cavallo morto alla fine di un decorso completamente prevedibile. Può capitare che si formuli una prognosi eccessivamente sfavorevole ed il cavallo riesca facilmente a sopravvivere per molti anni restando apparentemente sano; ciò può compromettere la reputazione del veterinario. La collaborazione da parte del cliente è uno dei principali aspetti della medicina di base dell'oncologia nel cavallo.

Summary

The basic principles of the diagnosis and management of the various common neoplastic diseases of horses will be discussed. Diagnosis is often made by intuitive supposition but in some cases this can lead to errors of judgement in therapy and prognosis. The value of biopsy is undisputed but in some cases it is not necessary (e.g. melanoma) while in others it may be specifically contraindicated (e.g. some forms of equine sarcoid). Some forms of treatment are logistically difficult to apply (e.g. radiation) while others are much easier (surgical excision of small focal melanomas) but some treatments carry serious risks to the operator or the horse or the environment (or combinations of these). Recent renewed interest in equine oncology has lead to some new treatments such as the use of cisplatin in squamous cell carcinoma and sarcoid or the use of cimetidine in the management of some cases of melanoma. There are dramatic improvements being made in the understanding of neoplastic processes in all species and although the horse is a generally poor model and clinical trials are difficult to undertake (for several reasons), some of these findings are providing better long-term opportunities for oncological treatments. However, there remain the severe limitations in the treatment options, which are mainly due to the size and the nature of the horse. Drugs are usually expensive and required in large amounts and so serious internal neoplasia is seldom amenable to therapy. For the most part owners expect a diagnosis and then a carefully considered prognosis. Veterinary surgeons should try to avoid making ill-considered statements about individual cases without first considering the whole horse and the owners ability / willingness to undertake the treatment offered. There is little worse than a large bill and a dead horse at the end of an entirely predictable course. An unduly poor prognosis may be given and the horse may easily survive for many years in an unaffected state and so the reputation of the vet may be harmed. Client handling is major aspect of the basic medicine of oncology in horses.

Neoplastic disease in the horse has some interesting features that are important. The skin is the major organ for neoplasia in horses – over 80% of all neoplastic disease in major surveys of tumour prevalence (carried out at slaughter houses or from academic institute pathology departments) involve the skin. There is a high incidence of local malignancy but a much lesser number of cases of aggressive metastatic tumours. With a few notable exceptions such as the pedunculated lipoma in older horses, neoplastic disease is more prevalent in younger horses than older ones. Many of the tumour types that affect horses have a their main importance in their secondary effects such as space occupying expansion or functional activity in the case of glands.

In order to formulate a rational therapeutic protocol for a neoplastic disease several major considerations must first be taken into account:

a) The exact nature of the condition
   i. Diagnosis of tumour
   ii. Primary effects of functional or space occupying nature
   iii. Secondary effects
b) The prognosis for the specific case, taking into account:
   i. Tumour type
   ii. Tumour locality
   iii. Tumour extent
   iv. Nature and type of the direct complications
c) The cost of treatment
d) The secondary effects of the treatment regimen

It is important that practicing veterinarians have a thorough understanding of neoplastic disease and the mechanisms for their aetiopathogenesis. Recent research in many different species confirms the multifactorial nature of the predisposing factors. There are significant contributions to the development of neoplastic disease in any organ system from genetic factors. There are many families of horses that are for example prone to equine sarcoid. The recognition of the process of apoptosis has led to an improved understanding of the immortality of neoplastic cells but the reasons for the mutation and alterations in behaviour are still not clear. Failure to recognise the abnormal cells may be a property of the cancer cells ability to hide itself from immune processes or the neoplastic process may impair the function of the body so that the abnormal cells are not treated as foreign.

Before embarking on any treatment the attending veterinarian must establish the true diagnosis. Many neoplastic lesions have a benign appearance while the true consequences may be much more serious than is thought art first. Similarly there are some non-neoplastic conditions that have all the outward appearance of certain of the neoplastic conditions; exuberant granulation tissue or bacterial pyogranuloma (pseuodomycetoma / botryomycosis) may closely resemble the fibroblastic sarcoid but the treatment for each is considerably different! This will necessarily involve the services of a pathologist skilled in the diagnosis of neoplastic disease of horses. There is a strong tendency to involve pathologists with general experience but in my experience there is little better than a qualified and capable equine neoplastic pathologist. The pathologist should be consulted early in the investigation of the case and although intuitive supposition is a significant diagnostic tool for many equine neoplastic diseases. It is certainly true however that with experience a reasonably informed “guess” can usually be made for many of the common neoplastic diseases such as squamous cell carcinoma, melanoma and equine sarcoid. Many other conditions may be much more difficult to diagnose and so a pathologist is a useful ally!

On first attendance the veterinarian needs to make a thorough clinical examination and obtain an extensive anamnesis (history). Failure to take these preliminary steps will usually result in significant difficulties later in the process and it is clearly better to do it at the first attempt. Without a full clinical examination (possibly even including a rectal examination and thoracic radiography and ultrasonography) many important aspects of the condition may be missed. Also there is the possibility of a dales diagnosis. Thus a horse with lymphadenopathy may be diagnosed with lymphosarcoma but in reality it may simply be a matter of an infectious process. Of course the contrary position could be just as serious – i.e. to make a casual diagnosis of a serious condition is possibly just as bad for the reputation of the vet! A rectal examination can for

example detect asymmetric enlargement of the iliac lymph nodes in a pony with a suggested diagnosis of penile squamous cell carcinoma and the implications from this are profound. Similarly a mare with a cutaneous histiocytic lymphosarcoma diagnosis could be found to have a Granulosa Cell Tumour and removal of the latter might result in at least partial resolution of the former.

The pathological consequences of a tumour are not always obvious. Tumours can exert their effects in several ways:

i. Space occupying effects

These effects are usually more prominent in slow growing, benign tumours but clearly can be significant in any sort of tumour. For example a common cause of exophthalmos is a lymphoma in the retrobulbar tissues.

ii. Endocrine effects
iii. Direct functional effects
iv. Local destructive/ invasive effects. For example an invasive and destructive tumour in the caudal parts of the nasal cavity or the caudal maxillary sinus can easily invade and destroy the thin plate of bone that separates the sinus / nasal cavity from either the brain or the orbit. In the former case central nervous signs may be encountered while in the latter a prominent (and often painful) exophthalmos will develop
v. Metastatic effects

Because many cancer therapies have serious implications on other / unrelated body systems and organs it is wise to make an extensive biochemical and haematological survey also at the first occasion even when a reasonably certain diagnosis can be made.

Diagnostic methods should be applied to all suspected cases of neoplastic disease. The range of diagnostic modalities include:

a. Radiography
b. Ultrasonography
c. Gamma scintigraphy

The value of a biopsy or tissue specimen is significantly enhanced by the provision of a full case description to the pathologist. This will likely enable the pathologist to make a significant contribution to the likelihood of treatment and to the overall prognosis. Thus is a veterinarian submits an excisional biopsy and the pathologist is told where it was obtained and the details of the case he/she may be able to report that excision was not complete and that further measures are likely to be required if recurrence or exacerbation are to be avoided. The diagnosis of malignancy is another area where the pathologist can help significantly. The main problem is however that many interpretations are derived by extrapolation from other species and in the horse this is probably most unwise. Thus for example a squamous cell carcinoma of the eyelid in a bovine is commonly malignant and readily metastasises to the parotid lymph node while in horses they are only very rarely malignant in this way.

Having established a diagnosis and likely prognosis the possibilities of treatment will need to been considered. In this aspect the welfare of the horse is paramount. Many cancer treatments have severe effects and the secondary consequences can be more severe than the primary disease. Thus a case of cutaneous histiocytic lymphosarcoma may survive reasonably well.

The secondary effects of neoplastic diseases are significant but there is little if any published material regarding the incidence and nature of the paraneoplastic disease in horses. There are anecdotal reports of reductions in performance but the reasons for this are difficult to establish. However, the main secondary effects include:

Clinical effects

- ❑ Weight loss and debility
- ❑ Reduced performance
- ❑ Laminitis
- ❑ Infertility
- ❑ Haemorrhagic diatheses

Biochemical / Haematological effects

- ❑ Anaemia
- ❑ Dysproteinaemia
  - ■ Hypoalbuminaemia
  - ■ Hypogammaglobulinaemia
  - ■ Gammopathy (monoclonal)
- ❑ Hypoglycaemia
- ❑ Hypercalcaemia
- ❑ Coagulopathy

It is clear that even small, apparently insignificant neoplasia can have profound systemic effects that may not readily be attributed to the possibility of neoplastic disease.

For each tumour type there are relatively few effective therapeutic options but correct selection can have a significant bearing on the prognosis. When considering the choice of treatment for any particular type of tumour the clinician should identify the best possible option for the particular case at the outset; neoplastic diseases are in general intolerant of partial treatment and commonly this results in exacerbation at best and dramatic metastases at worst. This should consider the specific nature and behaviour of the tumour type, the feasibility of the method *viz á vis* the patient and the facilities available, and the owners financial limitations. By careful selection of treatable tumours it is possible to maintain a 100% success rate but this usually means that no attempt is made to manage difficult or complex tumours in difficult or complicating sites. Clearly the oncologist with 100% success is not being challenged and will likely not be making a serious attempt to help seriously ill horses. Furthermore such an approach does nothing to improve our management of neoplastic disease in general. Incorrect selection will almost always result in regrets later while careful selection can deliver a very high percentage success rate overall. Even the correct (best) option can fail and then it is easy to retrospectively criticise the selection!

The underlying philosophy of "if you cannot do good then you must certainly do no harm" should be uppermost in the minds of any clinician dealing with neoplastic disease. Some benign lesions e.g. sarcoid tumours may become very aggressive when treated incorrectly. Furthermore failure is often accompanied by a reduced prognosis for subsequent attempts. This is particularly so for the equine sarcoid. In spite of the best-informed judgements as to the best modality, clinicians will inevitably face unusual responses either with failure to respond at all or an unexpectedly severe response / secondary complications or deterioration / exacerbation of the tumour.

Failure of a selected regimen tends inevitably to be problematical and second or "fall-back" options are not usually well tolerated. The easy option is often tempting but the underlying pathology and the secondary consequences are particularly unforgiving in and around the eye. For example squamous cell carcinoma of the eyelids can be extensive and surgical excision is seldom feasible; radiation is much preferred at this site. By contrast a proliferative or ulcerative / destructive lesion on the third eyelid is best treated by excision or by cryosurgery. The ultimate sanction against most neoplasia of the periorbital skin or conjunctival and corneal neoplasia is of course radiation but again some tumours such as melanoma are much less responsive or even completely non-responsive.

Furthermore there may be secondary consequences on adjacent normal structures (such as cataract or corneal opacity) when high doses of radiation are used. Accurate dose calculations are essential whenever radiation is used but there is little information on most of the equine orbital or periorbital tumours. The help of a clinical oncological physicist is advised.

In dealing with cancer therapy clinicians should always be aware of any health and safety implications from the materials being used. Apart from the surgical options most of the others can have severe and even life-threatening consequences on the operators. Radiation is the obvious concern but chemotherapeutic agents, including cisplatin or vincristine for example, can be equally dangerous when treated in an inappropriate way. Under no circumstances can cancer therapy of any type be considered to be without some sort of hazard for either the patient or the operator or both!

In equine oncology there are severe limitations in the selection of therapeutic options. Local lymph nodes are seldom accessible and although high malignancy is not common, the size of the horse and the species sensitivity to systemic oncological medication makes narrows the possibility very strongly. In the human and small animals oncological therapy

can be selected with a wider degree of freedom and the progress of treatment can be monitored much more simply. The costs are correspondingly lower. In many cases horses are destroyed on humane grounds long before any therapy is attempted and so the diagnosis of a malignant tumour is usually treated as death sentence.

In this paper the basic therapeutic options and management of the various types of tumour will be discussed and their respective advantages and disadvantages identified. Subsequent specialist papers will focus on the specific needs of particular tumour types.

a) Surgical excision is an attractive option for accessible benign, well-defined tumours at convenient sites. It is relative simple in uncomplicated cases. For example tumours on the nictitans and cornea are often amenable to surgical excision provided that the extent of the tumour can be defined and that suitable reconstructive surgery can be applied to restore normal function. However, surgical excision can be fraught with danger in some locations, such as the eyelid and the eye itself. The integrity of the eyelid margin is critical to its efficient function. Eyelid distortion can lead to serious and/or persistent corneal problems and so where the eyelid margin has to be interfered with due care must be taken to ensure that the marginal integrity is restored. Notwithstanding the obvious difficulties with surgical excision the periocular neurofibroma has been treated successfully by (repeated) surgical intervention (Pascoe, 1991) and some surgeons have had reasonable success with surgical excision of single nodular sarcoids. Surgical access to the retrobulbar tissues is extremely difficult and excision of tumours here is probably not possible. Surgery has also been successful in some internal neoplasia. Edwards (personal communication) successfully removed a large invasive lymphosarcoma from the jejunum and adjacent mesentery in a mature stallion. Histological reports gave a very poor prognosis but the stallion lived a normal life without any subsequent disability. Well-defined melanomas also are often amenable to surgical excision but again the results are unpredictable. Clearly there are tumours that are amenable to surgical excision and individual surgeons may have better or worse experiences with these. The correct decision for surgical excision must be based on the basic tenets of oncological surgery – the tumour must be able to be removed completely prior to the spread into inaccessible tissues or to the drainage lymph nodes (unless these are also removable) or metastases have occurred. For example a penile squamous cell carcinoma may be cured by amputation of the penis but this approach will be valueless if the preputial ring or iliac lymph nodes are involved at the time of surgery. The decision for surgery or other therapy must take account of the likely malignancy and the probable behaviour of any residual tumour after surgery has been completed.

b) Cryosurgical destruction of tumours is also a difficult procedure that can be catastrophic if either the margins of the mass cannot be defined or the true extent of the tumour is not defined. Furthermore the destruction of tissue tends to be indiscriminate and so during the procedure surrounding normal tissues are almost inevitably damaged. Therefore, this method suffers from the same consequences as surgical interference with respect to scarring and fibrosis but there have been reports of its successful use in various sites including the eyelid (Hilbert, 1977) and mouth. Notwithstanding the possible complications, small lesions have been successfully managed with focal cryonecrosis. For example, focal freezing of corneo-limbal squamous cell carcinoma, carcinoma in situ and eyelid / conjunctival melanomas is possible and can be very satisfying. However, control of the freeze-thaw cycles is critical if intraocular damage is to be avoided and while in theory thermocouples are required, their placement may be singularly difficult or inappropriate for some ocular tumours. Cryonecrosis is commonly used in skin tumour management – it is probably of little or no value for internal tumours. Fur-

thermore it is a time consuming procedure. Multiple tumours make the process almost impossible. There are several basic principles that have to be adhered to when using this method:

- **i.** The tumour extent must be definable
- **ii.** Thermocouples must be placed at the margins to ensure true freezing of the whole tumour
- **iii.** Freezing in three cycles must be completed with a rapid freeze and slow thaw process
- **iv.** The natural "central heating" mechanisms created by the blood flow to the tumour needs to be regulated or removed – this can be achieved in some locations with the help of a tourniquet.

Uncontrolled application of liquid nitrogen to the skin or uncontrolled and unmeasured application of a heat sink are totally unacceptable; when this is done in humans then it can be done on horses by humans! Commercial liquid nitrogen spray systems are available and work well when combined with thermocouple control of the freezing process. Freezing systems reliant upon nitrous oxide will never achieve the required temperature drop for long enough and so are useless for horses.

v. Hyperthermia (radiofrequency): I have limited experience with this method of management but there are reports of highly successful treatment of superficial verrucose or occult sarcoids, surface corneo-limbal squamous cell carcinoma and carcinoma *in situ* lesions. The method has been developed for eye cancer in cattle but it appear that it might be useful for horses and sarcoids in particular[1]. Its effects are due to the increased sensitivity of neoplastic cells to temperatures of 42°C - 46°C, which can be lethal to neoplastic cells. In theory at least the method is reasonably selective in its effect and so it is a pity that it has not been more widely tested.

[1] Ideal Thermoprobe, Neogen, Chicago Call Dr Schwink on 00-1-540-961-0768.

vi. Laser excision: The availability of CO_2-YAG laser units has limited the use of this method. There are clear advantages in its use but the selection of the cases is again critical. The advantages of laser surgery lie in the bloodless surgical field, the extremely fine control that is possible and the "cautery" of the incisional edges. However, the equipment is very expensive and use requires special precautions. There are reports of 60 – 80% success (Diehl et al., 1987; Vingerhoets et al., 1988; Palmer, 1989) but the cosmetic consequences are usually little better than sharp excision.

vii. Chemotherapy (direct and chemical cautery / antimitotic effects) has been used for many years in a variety of forms mainly in the management of cutaneous neoplasia. There seems little benefit from systemic antimitotic and cytodestructive drugs. Chemical caustic materials such as arsenic are entirely inappropriate for the eyelids but intralesional cisplatin and topical AW4 (which is based heavily on 5-fluorouracil) have been used with limited success in a few cases. Topical applications of 5-fluorouracil may be a useful method of treating residual carcinoma in situ or squamous cell carcinoma lesions. Systemic antimitotic and cytotoxic drugs are used widely in other species but have seldom been applied to horses. This is usually for the combined reasons of cost (the drugs are all expensive and require sustained high doses that make it prohibitive in horses) and lack of efficacy. There are few clinical reports of systemic treatment of serious internal neoplasia. All the drugs are also non-discriminatory and so have harmful side effects. In many cases these are unacceptable for horses. Nevertheless the future use of modern oncology drugs should be considered as and when suitable indications are presented. It is only by this expedient that progress will be made.

viii. Immunological methods: These rely upon the alteration of the immunological relationship between the host and the tumour cells. Any method that can establish a normal rejection mechanism will result in a dramatic and satisfactory resolution of the neoplasm. Interestingly in a few cases equine sarcoid

spontaneously disappears in some horses. The mechanism for this is unknown but it certainly provides a direction for future research.

Current oncological research is focusing on alteration of the immune mechanisms or alteration of the tumour cells, thereby making them immunologically recognisable. Targeted (monoclonal) antibody or antibody derived endogenously following the systemic introduction of recognisable tumour specific antigens may provide a means of therapy in the future. This mechanism is being explored in humans and horses in the management of melanoma. Although the nature of the tumour in the two species is considerably different with different implications for both prognosis and therapy, there has been some interest in the use of X-irradiated autogenous cultured melanocytes as a vaccine. The results are as might be expected very disappointing in horses and it clear that the mechanism does not apply when the tumour type is not a true neoplasm. For many years clinicians have attempted to manufacture autogenous vaccines from sarcoid cells. This is an entirely inappropriate approach given that the naturally occurring tumour does not induce any detectable immunological response. Furthermore the equine sarcoid should probably not be regarded as a virus disease. The presence of a "bovine papilloma-derived oncogene" within the cells of almost all sarcoids suggests a relationship but so far no vegetative virus has been discovered. Furthermore no horse with naturally occurring sarcoid has yet seroconverted to BPV-1 or any other related virus.

ix. Immunomodulatory therapy: Interestingly the value of autogenous vaccines is widely regarded as inappropriate but for certain nodular and fibroblastic sarcoids around the eye the results of BCG therapy are really good! The protocol for use appears to be important and repeated injections of a protein material are not without hazard. There have been reports of anaphylactic shock following injection of BCG. In my experience the secret to both success and safety is the true intralesional injection of the material. This may also explain why mixed, verrucose or occult lesions do not respond to this method as well. Interestingly the use of BCG in cattle squamous cell carcinomas has a reasonable prognosis but in the horse it has far less benefit. It is difficult to understand why this should be the case.

x. Novel therapies for tumours in horses: These include several different drugs including tazarotene, which can be used to control the secondary effects of the equine sarcoid. Recent work at Liverpool suggests that much of the verrucose and epidermal cell proliferation seen in equine sarcoid skin disease is a secondary change to abnormal / inappropriate epithelial cell growth factor (interestingly the same factor is induced by the equine papilloma virus). Restoring normal epithelial cell function enables the clinician to identify the primary sarcoid tumour foci and so target therapy at these areas alone rather than having to provide a blanket treatment for the whole area.

xi. Radiation: Ionising radiation destroys living cells and this property is employed to treat certain types of neoplasia. The application to ophthalmic medicine is important in providing a therapeutic option for tumours, which have otherwise no chance of resolution. The techniques have significant advantages in minimising scarring and distortion due to cicatrization in an area where the function of the organs involved is of vital importance.

The basic principle of the technique arises because ionising radiation (γ electromagnetic radiation) and high energy particles (α = helium, β = high energy electrons) ionise tissues through which they are directed. It is assumed that the major effect of the radiation is on DNA but it is likely that a wide range of cell proteins and lipids are affected within the cell and in the cell membrane. It is important to remember that the response to a radiation dose may be slow to develop. This is because the cells may survive in the absence of effective DNA but are unable to reproduce and therefore the natural ageing process of the cell type reflects the delay in clinical effect, which is characteristic of radiation therapy. Cells which have an inherently high replication rate e.g. one marrow cells would therefore be expected to show a faster response than those

with low natural mitotic rates e.g. bone and fibroblasts. In the case of bone the effect of radiation may only become apparent after months or years while bone marrow shows a dramatic response within days. This principle can be used effectively to alter the proportion of normal to abnormally dividing cells in a tumour mass - the faster dividing neoplastic cells being (at least in theory) more susceptible to radiation than the slower normal tissue.

The use of laser Doppler techniques has established that the blood supply to cutaneous tumours (at least) is abnormal - often reduced compared to the normal surrounding tissue. Thus tumours are often nutritionally deprived and mildly hypoxic which might render the tissues less susceptible.

Following a course / dose of radiation the tissues are destroyed (after a variable period) and then a process of repair needs to take place. Normal tissue needs to replace the destroyed areas from natural stem cells. It then needs to become reorganised into a natural and therefore functional organ system with restoration of blood supply and oxygenation.

Radiation is used in two basic ways:

1. Brachytherapy: This technique is used primarily for the treatment of superficial tumours which are either situated in areas which are not amenable to surgery, or which have recurred after previous attempts to remove them (by whatever means). Radiation sources are applied directly onto or into the mass. The most frequent methods for this include a number of sources of beta and gamma radiation which are implanted into the tumour mass or are applied directly to the surface. In the former case (e.g. iridium ^{192}, Gold ^{198}) gamma radiation is continuously emitted through the target tissue and the relative emissions and lengths of source can be adjusted. In the latter (e.g. Strontium^{90} plaque) the radiation is applied in fractionated doses calculated to deliver the required "lethal" overall dose. This is more important for β radiation than for γ radiation. The term brachytherapy also applies to radiation materials, which are introduced into the bloodstream with delivery to a target organ where it is deposited and accumulates in sufficient quantity to cause ionisation of cells. The latter technique is seldom used in horses but has become increasingly valuable as monoclonal antibodies are developed so that the radioactive "labelled" antibody has a specific target cell type to which it adheres. The process is elegant in concept but has inherent limitations. Iridium ^{192} sources are expensive and requires specialised facilities for stabling and care over the period of treatment which may be up to 10 days or more. Strontium ^{90} plaques are much easier/safer to handle but require fractionation and therefore repeated potential operator exposure. Strontium ^{90} has a better effect on superficial tumours than Iridium ^{192}.

Teletherapy (External Beam Radiotherapy): this is performed far less frequently in equine medicine, mainly for logistic and capital cost reasons. In this case X-rays of extremely high energy α, β or γ radiation is produced in a beam form (usually using a linear accelerator) and are directed from the source towards the tumour tissue. The relative penetration of the various radiation limit the effect and applications but multiple beams can be used to create a "radiation hot-spot" which with careful positioning can be very finely defined. Such a technique may be used to apply fractionated doses simultaneously i.e. single beams not being of sufficient power to damage tissues through which they pass but focusing at a central point where the combined power is sufficient to cause ionisation of the target DNA. Larger doses can be given and more extensive tumour cells can be destroyed in this way. Single beam applications usually require multiple fractionated doses and in most cases this would require repeated general anaesthesia making the procedure considerably more difficult and unsafe. It is also limited to use on distal limbs and the head.

Currently there are very few facilities with teletherapy that can be applied to the horse. Radiation brachytherapy is largely restricted to ophthalmic oncology and it is most frequently applied by brachytherapy in the treatment of squamous cell carcinoma, neurofibroma and nodular and fibroblastic sarcoid around the eye. There are few reports of the use of teletherapy for any other equine prob-

lem but Coombe (1994) (Equine Veterinary Education, vol 6. P91-92) described a case of an isolated parotid lymphoma, which resolved completely following repeated teletherapy. The condition is itself rare and other applications of teletherapy to other anatomical sites and tumour types might be more problematical. Radiation has a considerable advantage over most other tumour treatments in having a very acceptable cosmetic consequence. Scarring is minimal and the slower rate of resolution allows local tissues to adapt to changing cell types more easily. For this reason and because the procedure carries both cost and safety implications (no matter how it is applied) the technique is usually restricted to small tumours in difficult sites such as the eye and periorbital skin and over joints. There is the added advantage that radiation can be used as "fail-safe" technique - previous less expensive techniques which have not succeeded may still be treated by this method with good prospects of success. Radiation therapy carries a better overall prognosis than most other methods and can be combined with surgical debulking (such as in the treatment of corneal carcinoma in situ) so that less radiation needs to be applied. As the clinical effects of radiation depend heavily on the replication rate of the cells involved tumours growing fast are more responsive than old, long-standing tumours. The latter may take longer to respond and may need higher calculated doses of radiation than the former. In some tumours (particularly those involving bone or fibroblasts) the rate of replication of the tumour tissue may be less than the surrounding normal tissue and in these conditions the effect of radiation may be harmful rather than beneficial.

Teletherapy using a linear accelerator is possible and logical but is largely impractical - requiring general anaesthesia and fractionated doses daily (or 2 - 3 daily) for several applications. It is however very effective for most eye tumours (except melanoma).

The full effects of radiation treatment may take several months to become apparent. Tumours treated in this way often show a progressive size reduction for up to 12 months but in other cases considerable local necrosis occurs and abscess discharge may be alarmingly severe - horses should not be destroyed if the latter occurs!

a) Strontium^{90}: Pure β emitter, which decays to Yttrium^{90} over a half-life of 27 years. Strontium sources are available as plaques with a short handle behind a shield. β radiation has very high energy over a short distance with maximal penetration at 1 - 2 mm. This means that surgical debulking is usually required and the best results are obtained after this. Fractionation of the required/calculated dose needs to be carefully calculated to avoid excessive tissue damage. A dose of approxi-

Source	*Half-life*	*Emission*	*Notes*
Strontium^{90}	28 years	β	poor depth penetration / very limited effect; small tumours only; expensive
Ruthenium^{p}		β	poor depth penetration / limited effect; small tumours only expensive
Cobalt^{60}	5 years	γ	USER DANGER*. Effective; complex dosimetry; expensive; impractical
Cesium^{137}	30 years	γ	USER DANGER* Effective complex dosimetry; expensive; impractical
Iridium^{192}	72 days	β# γ	USER DANGER* Effective complex dosimetry; expensive.
Gold^{198}	2 days	β# γ	USER DANGER* Effective complex dosimetry; expensive
Radon^{222}	4 days	γ	Gas: USER DANGER* Effective complex dosimetry; expensive

usually absorbed by sheath (platinum wire) - effectively these are gamma emitters.
* special precautions must be taken to ensure safety of all personnel with special feeding/watering facilities for the patient so as to avoid human risk.

mately 10,000 rads is required and this means that an average plaque needs to be placed directly onto the mass for 6 - 8 minutes daily for 5 - 9 days. The procedure is entirely feasible and carries little or no radiation risk to the handler provided that the appropriate precautions are applied. Superficial eye lesions such as carcinoma in situ (corneal squamous cell carcinoma) are effectively treated under sedation and topical analgesia. The radiation acts by:

- Killing tumour cells left after debulking surgery
- Reducing/inhibiting vascular supply to the tumour bed

Complications are minimal with only occasional reports of corneal opacity (usually temporary) and corneal degeneration/ulceration.

b) Ruthenium: Plaques containing ruthenium are available commercially and are sutured in position over the lesion and left in situ for 3 - 5 days. In this case the dose of β radiation is not fractionated at all but the material has a much lower output and the risks are minimal. The plaques are extremely expensive but can be used over 4- 5 years. Placement requires a general anaesthetic and subsequent control of the emission from the lesion (although in reality the risks are extremely minimal). Horses may not tolerate the plaques and may require temporary tarsorrhaphy.

c) $Cobalt^{60}$ / $Cesium^{137}$: Tissue implants left in situ for 4 - 6 days providing continuous γ emissions. Cobalt emissions are 2x those of Cesium - they require even more stringent controls on use and contact personnel. Good effects on squamous cell carcinoma and sarcoid.

d) $Iridium^{192}$: Available as linear sources in single pin or hairpin arrangements. Each source is effective for 0.5 cm radius around it and lengths vary. Careful dosimetry studies should be used and only the minimal length consistent with the tumour extent should be used. Varying sizes of tumour can be treated using varying power of source but this becomes logistically very difficult. They are all very effective against fibroblastic and nodular sarcoid and squamous cell carcinoma of all types. Placement however is sometimes very difficult e.g. carcinoma in situ requires that the source is placed across the closed palpebral fissure and left in situ for 5 - 10 days. Corneal edema and cataract have been reported when eyelid tumours have been treated with radiation brachy and teletherapy.

e) $Gold^{198}$: Both β and γ rays are emitted but the former are usually absorbed by the sheath. Available in pellet form. Special applicator gun is required and high-energy rating makes it difficult to handle. However it is effective against squamous cell carcinoma, fibroblastic and nodular sarcoid and neurofibroma. Cost is prohibitive.

f) $Radon^{222}$: Radioactive gas with a half-life of 4 days. Emits γ radiation only. Difficult to manage and high operator risk. Impractical.

TOXICITY/HAZARDS OF RADIATION THERAPY

> THERE IS NO HORSE
> WORTH YOUR TOENAIL
>
> - Never mind your bone marrow!

These can be divided into the acute or immediate effects, which are usually (hopefully) restricted to the treated case (rather than the operator). The skin surrounding the radiated tissue becomes inflamed (swelling, heat, pain and redness). The fastest dividing cells in the area show the earliest effects with superficial sloughing. In the case of the eye there may be a degree of corneal oedema over the treated area of cornea. The reason this is not more severe is that the superficial corneal epithelium has much less significance on corneal oedema than damage to the deeper endothelium. Thus β emission from $Strontium^{90}$ probably does not penetrate enough to cause deep damage and therefore marked corneal oedema. The use of $iridium^{192}$ at this site (usually applied across the closed eyelids) does have much higher penetration and therefore induces more severe corneal oedema. In either case the damage is transient - resolving within days or weeks.

Chronic effects of radiation are more obvious. They may have significant implications for operators who are repeatedly exposed to radiation of any description. These changes affect slowly dividing cells e.g. bone, cartilage and lens. Thus damage to the lens culminating in the development of cataract can be a secondary consequence of gamma radiation in and around the eye. However, it would seem that in reality this risk is minimal. At the Philip Leverhulme Hospital, Liverpool University, of 56 horses subjected to Iridium treatment for eyelid or orbital squamous cell carcinoma and sarcoid tumours none have developed any evidence of cataract after periods ranging from 6 months to 15 years. Radiation has significant effects on melanocytes and hair follicle germ cells. Therefore radiated sites commonly develop both alopecia and leukoderma/leukotrichia. Only in very rare cases is there any apparent long-term effect on local cell repair and restoration of function is to be expected in almost all cases (unless the radiation dose is excessive).

Repeated exposure to ionising radiation has potentially disastrous consequences for operators including the development of internal malignant neoplasia.
Unless specific reasons exist and suitable precautions can be taken other means of treatment should be explored.
Radiation is a dangerous last-ditch resort even though it has very satisfying results for the most part!

Definitions encountered in Radiation/Nuclear Medicine

α **emission**: Helium atoms under high energy (easily stopped by a sheet of paper) - very low penetrating power but high energy

β **minus particle**: β energetic particle (high speed electron). Higher penetrating power than α particle but can be stopped by a sheet of plastic or several sheets of cardboard.

γ **-ray**: Penetrating high energy electromagnetic emission from a radionuclide

Becquerel (Bq): unit of radioactivity (equivalent to one disintegration per second)

MBq = 10^6 Bq (the unit for radionuclide activity) (37 Mbq = 1mCi in old units)

Gray (Gy) unit of absorbed dose, 1 joule/kg

mGy: 10^{-3} Gy = 0.1 rad (old units)

cGy: 10^{-2}Gy = 1 rad (old units)

e.d.e.: Effective dose equivalent, expressed in milli Sieverts (mSv)

Sievert (Sv): Unit of effective dose equivalent, numerically the same as the Gray (Gr); 1mSv = 100 mrem (old units)

Half Life / T_1: Radioactive decay is such that the number of unstable atoms disintegrating (and hence the quantity of radiation emitted) decreases exponentially with time. The quantity is halved in a characteristic time for each nuclide (the half life). Residual activity can be calculated from the half-life.

Radioisotope / Radionuclide: A nuclide of artificial or natural origin that exhibits radioactivity. Atoms of all elements are composed of individually defined arrangements of atomic particles (protons, electrons, neutrons). Nuclides containing the same number of protons (equivalent to the atomic number) have the same chemical properties and are known as isotopes. Atomic mass numbers are determined by the number of neutrons also present in the nucleus of the atom. Radionuclides produced by reactors contain excess neutrons while those produced in linear accelerators (cyclotron) are deficient in neutrons. The most prevalent isotopes of an element are usually the stable ones and are naturally occurring. Radio-isotopes are the unstable isotopes of an element which tend to decay or revert to stable forms and in so doing emit radiation. A radionuclide is a specific radioactive atom designated by indicating the element and its atomic mass number e.g. Iodine-131 = I^{131}. The radiation emitted by such an element enables the detection of extremely small masses, below the limits of clinical detection and so these elements can be used as tracers in the body without disturbing the adjacent tissues. The radiation emitted by a particular isotope is characteris-

tic and unique - with fixed decay characteristics and emission spectra (rate, type and energy of emission). Radionuclides may emit α, β or γ radiation. Beta minus particles are easily absorbed by tissue but are less useful for therapeutic means unless by very intimate contact/proximity. Gamma radiation are more easily transmitted through tissues and have a more profound ionising effect on the chemical of the target cells. The faster dividing cells are characteristically more rapidly affected but it is vital to remember that all cells will suffer to some extent.

Labelled Compound: One in which a proportion of the atoms is radioactive or to which a radioactive compound has been chemically bound.

Specific Activity: radioactivity per gram of stable material.

Radiopharmaceutical: Any material containing radionuclide administered to a patient for test or therapeutic purposes.

Tracer dose: A small quantity of a specific radionuclide, which is administered to determine but not affect the natural metabolism.

Therapy dose: A large quantity of radionuclide administered for the purposes of radioactive destruction/alteration of tissue.

Gamma camera: Scintillation camera, which can image the emissions by accumulation onto sodium iodide. It only works for gamma emissions.

Point camera: Scintillation counter applied to the body for defined periods during which the number of emissions can be counted accurately.

Scintillation: The process in which ionising radiation is converted to visible photons.

TREATMENT OPTIONS

TYPE of TUMOUR		Site	*SURGERY* Sharp	Cryo-	Hyper-therm	YAG Laser	Immune BCG[1]	Chemotherapy 5-FU[2] / AW4	Cisplatin[3]	Systemic[4]	Radiation β[5]	γ[6]
Sarcoid	occult	PS	+	++	++	++	N/A	+++	N/A	(N/A)	++++	++++
	verrucose	PS	+	+	+	+	0	++	N/A	(N/A)	++	++++
	nodular	PS	+	+	N/A	++	+++	N/A	+++	(N/A)	N/A	++++
		E	+	N/A	N/A	++	++	N/A	++	N/A	N/A	++++
	mixed	PS	CI	+	+	+	+	+	+	(N/A)	+++	+++
		E	CI	CI	CI	–	+	+	N/A	N/A	+++	++++
	fibroblastic	PS	CI	0	0	+	++	0	++	(N/A)	N/A	++++
		E		CI	CI	–	++	N/A	++	N/A	N/A	++++
	malevolent	PS	CI	CI	0	0	0	0	0	0	0	0
Neurofibroma		E	++	+	N/A	(+)	+	N/A	++	N/A		+++
Melanoma		E	++	++	N/A	++	#	N/A	+++	++[8]	0	0
		O	N/A	N/A	N/A	N/A	#	N/A	N/A	++	0	0
		G	(+)[7]	N/A	N/A	(+)	#	N/A	N/A	N/A	0	0
Squamous Cell Carcinoma.	Prolif	E	++	++	+	++++	0	++	?	N/A	++++	++++
		Conj	++++	++	N/A	+++	0	?	?	N/A	++++	(+++)
		Corn	++++	+	N/A	+++	0	?	?	N/A	++++	(+++)
		3EL	++++	++	+	++++	0	?	?	N/A	++++	(+++)
	Ulcer / destruct	E	C/I	+	N/A	+	0	?	?	N/A	(++++)	++++
		3EL	++++	+	N/A	++++	0	?	?	N/A	N/A	N/A
Lymphoma		O	CI	N/A	N/A	N/A	N/A	N/A	N/A	?	N/A	+?

KEY TO ABREVIATIONS:

Prolif = proliferative; Ulcer/Destruct = Ulcerative and / or destructive; PS = periorbital skin; E = eyelids (palpebral); O – orbital; G = globe / ocular; Conj = conjunctival; Corn = corneal; # results of new research on irradiated autogenous vaccines awaited; N/A = non applicable or no reports of use in this way; CI = contraindicated in the authors experience

[1] As an intralesional injection repeated over some weeks.
[2] Topically applied as a 5% water soluble cream
[3] Administered as emulsion made up with equal volumes of cisplatin aqueous solution and sterile almond or sesame oil.
[4] Using vincristine or cyclophosphamide or other systemic antimitotic
[5] Delivered via a strontium^{90} plaque
[6] Delivered via brachytherapy using iridium^{192} or gold^{198} or via teletherapy by linear accelerator
[7] A specialist procedure not undertaken lightly!
[8] Cimetidine per os is reported to be helpful in some cases (Gotz et al. 1990)