



Carcinoma

Primary squamous cell carcinoma is a common tumour of horses that is restricted to squamous epithelium (skin, mouth, nasal cavity/sinuses, stomach). Within the broad pathological group there is wide variation in the prevalence of each type. Penile carcinoma is probably the commonest form encountered in horses.

The histological characteristics are typical and easily recognised. The extent of malignancy is easily recognized by the extent of differentiation and the character/normality of the keratin production. The less aggressive the tumour, the greater the normality and the greater the extent of production of keratin. Highly malignant forms produce virtually no keratin and have a particularly aggressive nature with rapid metastatic spread via blood and lymphatics to either remote organs or to the local draining lymph node.

What causes carcinoma?

Solar radiation, geographical location, and individual susceptibility (which may relate to breed, age and lack of adnexal pigment) are probably the most important risk factors of carcinoma. Predispositions occur within breeds (the Clydesdale Horse is probably predisposed) and within colour variations.

Depigmented skin exposed to carcinogens such as smegma (in the case of penile and clitoral forms) and sunlight (in cutaneous and ocular forms) are implicated but there are no scientific studies that confirm this widely held belief. Most clinicians will recognize that certain animals including coloured and cream ponies are predisposed



Perianal Squamous
Cell Carcinoma

Where does it occur?

There are some susceptible sites but by definition primary carcinoma has to occur where the cell type exists! This is the skin and the mucous membranes of the mouth, throat, upper airways (nostrils, nasal cavity and sinuses) and the stomach.



Skin sites	Respiratory Tract	Alimentary Tract	Reproductive Tract
Facio-nasal	Nasal	Oro-palatine	Penile
Palpebral	Paranasal Sinuses	Oro-pharyngeal	Vulval
Conjunctival	Nasopharynx	Gastric	Clitoral
Corneal		Anal	
Perineal			

Forms of carcinoma

From a purely clinical perspective three major forms of the disease are recognised.

1. Proliferative forms in which the tumour develops in a proliferative fashion. A common site for this type is the penile form in older geldings and the carcinoma in situ on the cornea.
2. Ulcerative/Destructive forms that result in tissue loss and erosions and ulcerations. These are commonly found for example on the non-pigmented eyelids and third eyelids. It is also the predominate form in perianal or perineal forms of the disease (as opposed to the vulvar form in mares)
3. Combined ulcerative/Destructive forms are actually quite common and are typified by the vulvar or clitoral forms. Younger geldings are liable to this form and where it occurs in horses under 10 years of age there is a very high degree of malignancy associated with it.

Ocular and Periocular squamous cell carcinoma

Squamous cell carcinoma (SCC) occurs in the eyelids, the conjunctiva (particularly of the third eyelid and the lateral limbus of the eye) and on the surface of the cornea (carcinoma in situ). Palpebral SCC (pSCC) is often extensive, highly destructive, and invasive. However, a milder proliferative, slower growing form is sometimes encountered. Non-pigmented eyelids are much more liable to develop the destructive and ulcerative form, and certain breeds seem more liable to its development. Although for the most part SCC of the eyelids and orbital structures are very seldom malignant, they can cause extensive destruction or infiltration and so treatment becomes progressively more problematical.



The least common ocular forms include a lateral limbal form that is invariably proliferative (at least until the condition is advanced), and a carcinoma in situ where the corneal epithelium is involved. The latter are sometimes difficult to diagnose. Usually cases are presented for investigation of ocular discharges (usually with a characteristic purulent appearance).

Clinical diagnosis is usually simple when the changes are advanced. In the early stages lacrimation is a feature, testing the tears with a urine blood dipstick usually reveals blood. Sometimes the lacrimation is plainly haemorrhagic. Pathological diagnosis of all the forms is easily achieved by biopsy but some sites are not amenable to excision of large pieces of tissue so pathologists need to be informed of the nature of the lesion and the location of the biopsy within it.

Cutaneous squamous cell carcinoma

Cutaneous forms of squamous cell carcinoma occur in the facial region, the ears and the perineal skin. The large majority of these are ulcerative/destructive forms. The site and extent of tissue loss at the time of initial presentation dictate the prognosis.

Penile squamous cell carcinoma

A pre-cancerous change in the skin of the penis and the glans may be detectable – usually such cases are presented for investigation of a preputial discharge (often containing some (stale) blood). There are two major forms of penile squamous cell carcinoma.

- The common form occurs in old geldings – stallions are very rarely affected and this suggests that smegma may be a significant carcinogen. The lesions may be proliferative or ulcerative/destructive or there may be a combination of the two. The glans is most often affected while the preputial reflection and the skin of the shaft of the penis may sometimes be involved. Lesions may be multiple and may be ulcerated or proliferative.
- In younger horses (<10–14 years of age) there is a much higher malignancy rate and these cases are often beyond treatment on presentation. Often the glans is the primary lesion.

The more malignant forms and those that have a very chronic course may sometimes “seed” into the skin at the preputial ring or preputial orifice. These lesions are very aggressive and may occur independently of the penile forms. The prognosis for these cases is extremely poor (en bloc resection of the penis and the prepuce with perineal



urethrostomy is the only therapeutic course of action to take). The site may become strictured by a combination of fibrous tissue scarring and tumour expansion, so the first signs of this complication may be difficulty with urination.

Vulvar/clitoral squamous cell carcinoma

Vulvar or clitoral forms occur almost exclusively in older mares. It is suggested that the carcinogenic properties of smegma may be involved in the development of the clitoral form. At this site carcinomas can develop on pigmented skin. The vulvar forms are usually proliferative when they develop within the vestibule, and ulcerative when they involve the lips of the vulva. The clitoral form is invariably proliferative. Treatment is usually a combination of radiation (where feasible and available) and surgical excision.

Mucosal squamous cell carcinoma

Squamous cell carcinoma can occur in any squamous epithelium. The commonest sites for these forms are in the oral and nasal cavities (including the paranasal sinuses) and the in the pharynx. The main presenting signs include chronic serosanguinous/fetid nasal discharge or oral bleeding. Secondary signs including nasal obstruction in the nasal forms and dysphagia in the oral forms. The clinical signs may not be obvious. Because these forms are usually proliferative (at least to some degree) facial distortions and swellings may be detected. These forms often have an aggressive destructive nature and so it is possible to have a large proliferative lesion with extensive surrounding destruction.

Gastric carcinoma

Gastric squamous cell carcinoma can only occur in the oesophageal (squamous) portion of the stomach. The suggested carcinogens include recurrent gastric infestation with *Habronema* and *Draschia* spp. worms or *Gastrophilus* spp (Bots) but there are many horses with high infestations of all these that never develop any pathology let alone carcinoma. There is no evidence in horses of a bacterial carcinogen. Usually the lesions are a combination of proliferation and destruction and this is probably the most aggressive form of the condition in horses. There is a high rate of direct spread to the liver and secondary metastatic spread to the lungs. The initial signs are not usually obvious and so on presentation these cases are usually clinically ill with weight loss, recurrent anterior abdominal pain and inappetance. The horse may be marginally anaemic; but usually recurrent colic, weight loss and a harsh dry coat are the main signs. Because these signs are



often attributed to other conditions and as a long endoscope is required for diagnosis, cases are often presented late in the course. It is sometimes possible to obtain a tentative diagnosis from gastric washings (containing both blood and abnormal squamous cells) or from peritoneal fluid (containing blood, protein and abnormal squamous cells that should definitively never appear in peritoneal fluid – usually in the latter cases there are reactive mesothelial cells also and so the diagnosis may be confused with mesothelioma or a simply a reactive peritoneal cavity.

Treatment of Carcinoma

Established SCC is usually locally aggressive and the prognosis is poor if periocular and/or orbital tissues have been invaded. SCC of the upper and lower eyelids can be treated by surgical excision/de-bulking combined with cryotherapy (usually a double freeze-thaw cycle with liquid nitrogen) or brachytherapy (usually via a strontium-90 applicator).

***Note:** Laser therapy has been used to treat a variety of equine eyelid tumours, but that it is too early to assess the overall long-term success rate.*

The management of squamous cell carcinoma relies upon surgical removal or cryonecrosis, or to the application of various antimitotic and cytotoxic chemicals. **Radiation is the gold standard** of therapy in suitable sites where surgical removal cannot be contemplated, or where the tumour margins cannot be defined sufficiently to allow total removal. There are no immunological methods for the management of this tumour type.

Radiation

Radiation treatment is probably the **best available option for all forms of SCC** in the horse but in the periorbital region there are logistic complications that significantly reduce its value much less. SCC is very susceptible to both gamma and beta radiation. Gamma radiation is used extensively (via linear iridium¹⁹² sources) in Liverpool for the treatment of palpebral forms of SCC. Beta radiation delivered via a Strontium ⁹⁰plaque has also had considerable benefit on limbal, Nictitans and carcinoma in situ lesions. **The cosmetic effects of the treatment are remarkably good** with a relatively rapid resolution and minimal secondary complications even in severely destructive eyelid cases. The relatively poor penetration of beta radiation (limited to 1–2 mm deep) means that surgical treatment may need to be applied before application of radiation (every piece of tissue removed from a surgical site should be submitted for histopathology so that rational treatment/dose calculations can be made).



Wherever possible, radiation should be considered to be the definitive method and is a useful fall back method when others are either not feasible or fail to resolve the problem.

Surgical excision

This is a realistic proposition for nictitans and conjunctival forms and for most cases of early penile carcinoma; indeed it is the treatment of choice for all defined types of carcinoma at all sites but the **criteria for selection of this method are strict**. Surgical removal of corneal *carcinoma in situ* is extremely difficult, requiring microsurgical techniques involving a superficial keratectomy of the affected area and a margin of 1–2 mm.

Eyelid tumours are seldom amenable to this option. Very small, localised and proliferative eyelid lesions can be excised if the margin of the lid can be preserved or can be reconstructed satisfactorily to preclude the complications arising from poor eyelid function. Surgical amputation of the penis in suitable cases is curative and recurrences are rare provided that the surgery is properly performed and that all the tumour tissue is removed. Attempts at en bloc resection for cases of aggressive carcinoma carry a correspondingly poor prognosis because the surgery is a temporary salvage procedure in most cases. Clitoral and some vulvar forms can be surgically removed with a reasonable prognosis.

Surgical ablation should not be contemplated if the tumour has already invaded the local lymph node or there are difficulties with margin definition. *Some sites totally preclude surgical removal.*

Cryosurgery

This is a fast but rarely effective method of treatment for eyelid lesions and small lesions elsewhere. Nasal lesions and some oral lesions may be managed in this way, but the results are dependent upon the surgical efficiency of total tumour ablation. Thermocouple assistance is obligatory. Lesions that are ulcerated and which bleed significantly can be managed by careful cryosurgery. Nictitans, limbal SCC, and carcinoma in situ have all been treated by cryosurgery with variable successes. **The secondary effects of the freeze may be very serious and so its use should be strictly restricted to small eyelid lesions and to limbal superficial lesions.** There are areas where this is totally impossible.

5-Fluoro-uracil

The value of this chemical in ointment formulation has been described for oral SCC (Patterson, 1997) but there are no reports of its use in the eyelids or for ocular lesions – it



would seem that this is an area that could have some prospect. A 5% solution of 5-F-U has been used by the author to treat a small limbal carcinoma that regrew at the site of a previous surgical excision but the true nature of the lesion (carcinoma V granuloma) was never established pathologically. **Topical 5-FU requires persistent application over some weeks or even longer**, and highly invasive or aggressive lesions do not seem to respond effectively in the time available. The commercial ointment is 5% but it may be that this is too weak to control a large or difficult lesion.

Cisplatin

Intralesional infiltration of an emulsion of cisplatin in almond (or sesame) oil or a stable emulsion containing a higher concentration of cisplatin can be used. It is effective in some cases although there are few reports of efficacy compared to other standard methods. **The method is difficult logistically** because the material needs to be injected intralesionally in a stable form. 1 mg cisplatin needs to be delivered to 1 ml of tumour. The volume and concentration of the chemical are critical. A stable emulsion is difficult to obtain in some cases because of the lack of water solubility of the chemical and the need to use an aqueous solution.

Immunomodulation using BCG

The author has had little success with this approach, in stark contrast to its value in the treatment of bovine ocular and periocular SCC. The reasons for this are not clear. **This is not of any value in sites away from the eye.**

Prognosis

The prognosis for squamous cell carcinoma is dependent on:

1. The site of the lesion and its suitability for any effective therapy
2. The malignancy of the tumour itself
3. The duration of the lesion and failed attempts to treat it
4. The extent of secondary consequences arising from the tumour.

For the most part SCC in the horse has less malignancy than in other species. Gastric carcinoma, oropharyngeal carcinoma, and penile carcinoma in younger geldings are usually (but not invariably) far more malignant than the others.



The prognosis is heavily dependent on the time interval between onset and diagnosis. An early diagnosis is critical, but the clinical signs are usually not distinctive and could easily be missed.

Tumour markers would seem to be the future hope for early diagnosis but as yet no specific (or non-specific) marker has yet been identified for horses. Until we have methods for early diagnosis and better treatments (with radiation teletherapy being the best overall option) the SCC is likely to provide both a diagnostic challenge and a therapeutic problem.