Available online at www.ijrbp.net

DOI: http://dx.doi.org/10.18782/2322-0392.1280

ISSN: 2322 – 0392

Int. J. Rec. Biotech. (2020) *8*(1), 1-24

Review Article

International Journal of Recent Biotechnology

Histological, Cytological Characteristics and Treatment Options on Common Skin Tumors of Domestic Animals: A Review

Mesfin Mathewos[1], Tilaye Demissie[2], Haben Fesseha[1*] and Metages Yirgalem[3]

[1] School of Veterinary Medicine, Wolaita Sodo University, Ethiopia

[2] College of Veterinary Medicine, Addis Ababa University, Ethiopia

[3] School of Veterinary Medicine, Haramaya University, Ethiopia

*Corresponding Author E-mail: tseyon.h@gmail.com

Received: 23.01.2019 | Revised: 27.02.2020 | Accepted: 4.03.2020

ABSTRACT

Skin tumors are the most frequently diagnosed neoplastic disorders in domestic animals and are caused because of exposure of the skin to the external environment. Chemical carcinogens, ionizing radiation, and viruses all have been implicated, but hormonal and genetic factors may also play a role in the development of cutaneous tumors. The complex nature of skin, which is made of various epithelial, mesenchymal, neural, neuroectodermal tissues and as well species being many in animals makes classification of tumors in veterinary medicine controversial. The most common skin tumors in domestic animals are equine sarcoid, squamous cell carcinoma, lymphosarcoma, melanoma, basal cell tumor, papilloma, mastocytoma, and canine transmissible venereal sarcoma. Tumors of domestic animals are commonly diagnosed via fine-needle aspiration cytology and histopathology in many countries while immunohistochemistry, radiology, ultrasound and detections of tumors markers are also used in well-equipped laboratories especially to detect metastasis. The treatment options for skin tumors are mainly based on types of tumors with surgical excision followed by radiation therapy, cryosurgery, and chemotherapy are among others. This review paper is organized to give a brief review of common skin tumors of domestic animals and their histological and cytological characteristics and treatment options.

Keywords: *Cytology, Domestic animal, Histology, Skin tumor.*

INTRODUCTION

Tumor is an abnormal growth or mass of tissue, but not always forms a mass and some of which include tumor of hematopoietic cells and carcinoma *in situ* (Birbrair et al., 2014; Cunningham, Fiebelkorn, Johnson, & Meredith, 2011). Tumor of skin and subcutaneous tissues are the most frequently recognized tumors in domestic animals. Skin tumors are relatively frequent, especially in dogs, horses, cattle, and cats. However, there is a variable incidence, and tumor types in different species of domestic animals (Constable, Hinchcliff, Done, & Grünberg, 2016; Dietz & Wiesner, 1982).

Cite this article: Mathewos, M., Demissie, T., Fesseha, H., & Yirgalem, M. (2020). Histological, Cytological Characteristics and Treatment Options on Common Skin Tumors of Domestic Animals: A Review, *Int. J. Rec. Biotech*. *8*(1), 1-24. doi: http://dx.doi.org/10.18782/2322-0392.1280

Copyright © Jan.-March, 2020; IJRB

International classification of disease (ICD-10) classifies tumors into four main groups: benign tumors, *in situ* tumors, malignant tumors, and tumors of uncertain or unknown behavior (Birbrair et al., 2014). However, when it is in skin the classification of tumors is difficult due to the complex structure, as well as to the ectodermal and mesodermal origin of skin components, to which structural and physiological peculiarities of the skin in different animal species and breeds are added (Baba & Câtoi, 2007). The classification of primary skin tumors is mainly histological, also taking into account the origin of structures (Goldschmidt & Hendrick, 2002; Goldschmidt, 1998). Skin tumors can be classified as follows: Primary tumors (surface epithelial tumors, basal cell and adnexal tumors, dermal and subcutaneous tumors, melanogenic system tumors and hemolymphopoietic tumors), secondary tumors or metastases and pseudotumors or hyperplastic skin lesions (Baba & Câtoi, 2007).

Regarding the etiology of skin tumors, the possibility of the intervention of intrinsic and extrinsic risk factors is considered, such as hormonal conditions, genetic and immunological factors, solar radiation, and ionizing radiation, viral and chemical factors (M. H. Goldschmidt, 1998). Prolonged and continuous exposure to sunlight is the best known etiologic factor, and a sunlight-induced skin tumor (carcinoma) relationship has been established in several domestic species. The sunlight associated tumors in animals include squamous cell carcinoma of the pinnae and external nares in white cats (Dorn, Taylor, & Schneider, 1971), squamous cell carcinoma of the eye and periocular structures in white-faced cattle, notably of Hereford breed (Hargis, Thomassen, & Phemister, 1977), carcinoma of the vulva in sheep and Ayrshire cattle (Burdin, 1964), carcinoma of the perineum in goats (Ramadan, 1975), carcinoma of the ear and other areas poorly covered by wool in sheep, carcinoma of the non-pigmented glabrous skin of the ventral abdomen in dogs (Hargis et al., 1977), and possibly horn carcinoma in Indian Zebu cattle (Naik, Balakrishnan, & Randelia, 1969), tumors of the skin, most notably papillomas and sebaceous adenomas (Priester, 1980).

Diagnosis in skin tumors is mainly made by classical histological methods. The improvement of these methods, complemented by immunohistochemical and electron microscopic examinations allows a higher accuracy regarding staging and in particular malignancy, prognosis and the most adequate treatment. Among diagnostic investigations, chemotherapy can be used either systemically as a primary method for treatment of a malignant tumor or as an adjunct to surgery or radiation therapy (Villalobos, 2011).

In the skin, radiation is most commonly used to treat round cell tumors (eg, histiocytomas; amelanotic melanomas; cutaneous lymphosarcomas; mastocytomas and transmissible venereal diseases) or solid tumors that cannot be excised completely (Baba & Câtoi, 2007). Although generally palliative, long remissions may sometimes be obtained with radiation therapy. Other forms of therapy include hyperthermia, laser therapy, photodynamic therapy, antiangiogenic therapy, metronomic therapy, gene therapy, immunotherapy, and multimodal therapy using a combination or sequencing of various therapies. In veterinary medicine, treatment of skin tumors, as well as that of other tissues and organs, is also conditioned by the economic factor. Thus, the therapeutic approach involves some restrictions (Villalobos, 2011). Thus this paper was prepared to give an insight on the frequency, histological and cytological characteristics and theraputic approaches of common skin tumors in domestic animals.

2. COMMON SKIN TUMORS IN EQUINE

The most common cutaneous tumors are equine sarcoid, squamous cell carcinoma (SCC), melanoma, fibrosarcoma, and cutaneous lymphosarcoma, respectively (Scott, Miller, & Griffin, 2001; Taintor & Schleis, 2011). Factors that have been associated with these conditions include ultraviolet radiation,

inflammation, trauma, and viral infections (Wobeser et al., 2010).

2.1. Equine Sarcoid

Skin tumor is the most common type of tumor diagnosed in horses, accounting for 45 to 80% of all tumors diagnosed (Knottenbelt, 2003). Sarcoids are locally invasive, fibroblastic skin tumors and represent the most common tumor in equids worldwide (Cotchin, 1977; Marti, Lazary, Antczak, & Gerber, 1993) and has been reported in horses, donkeys and mules (Marti et al., 1993) with an incidence ranging from 12.5 to 67% of all tumors (Baker & Leyland, 1975; Taylor & Haldorson, 2013b).

Bovine papillomavirus (BPV) types 1 and 2 are causally associated with the development and pathogenesis of equine sarcoids which represent the only known cross-species papillomavirus infection (Lunardi et al., 2013). There are 6 distinct types of sarcoid based on gross appearance and clinical behavior including occult, verrucous, nodular, fibroblastic, mixed and malevolent (Knottenbelt, 2003).

Occult sarcoids are flat and alopecic with mild scaling. Verrucous sarcoids are wart-like and have a raised, scaly, lichenified appearance with epidermal thickening. Nodular sarcoids are firm, well defined, subcutaneous lesions while fibroblastic sarcoids are fleshy and ulcerated with local infiltration. Mixed sarcoids may include any, or all, of the aforementioned types and often become progressively more aggressive as fibroblastic transformation occurs. Finally, malevolent sarcoids are the most infrequent form and are aggressive, invasive tumours that proliferate rapidly and may spread along fascial planes and vessels. Sarcoids can develop in any location, either as a single tumour or as multiple tumours of different type. The most common locations for sarcoid development include the head (periorbital region, ear pinnae and lips) and neck (39%), extremities (35%) and ventrum (26%) (Knottenbelt, 2003).

Inactive sarcoids may become aggressive if disrupted by injury, biopsy or inappropriate treatment. Although sarcoid tumours do not metastasis they can significantly impact the function and aesthetics of affected equids based on tumour location, size and frequency. Thus, the value of sarcoid-bearing equids is often dramatically decreased. Sarcoid tumours may cause discomfort and can result in ulceration, infection and occasionally lameness associated with lesion location (Taylor & Haldorson, 2013b).

Fig. 1: Fibroblastic sarcoid
Source (Hewes & Sullins, 2009)

Histologically, most lesions are composed of a thickened epidermis with prominent epithelial pegs that extend into a dermal proliferation of fibroblasts that are arranged in whorls, tangles, or herringbone patterns and contain small amounts of collagen. Nuclear pleomorphism and mitoses vary, but can be pronounced in rapidly growing or recurrent tumors (M. H. Goldschmidt, 1998). Surgical biopsy can definitively diagnose sarcoids, but there is a significant risk of making sarcoids worse. Therefore, diagnosis based solely on clinical signs, fine-needle aspiration or complete excisional biopsy are safer choices (Knottenbelt, 2003).

Currently, there is no uniformly effective therapy for equine sarcoid. Surgical management (including conventional excision and carbon dioxide [CO_2] laser excision), cryotherapy, hyperthermia, radiotherapy, chemotherapy, immunotherapy, topical immune modulation and antiviral agents are used with variable degrees of success (Wobeser et al., 2010).

2.2. Equine Squamous-Cell Carcinoma

Squamous-cell carcinoma is the second-most prevalent skin tumor in horses accounting for 12 to 20%. SCC results from transformation and proliferation of squamous, epidermal skin cells that become keratinized and are often solitary slow growing tumors that cause extensive local tissue destruction. Usually occur in horses greater than 9-years-old (Taylor & Haldorson, 2013a). SCC can appear anywhere on the body, but they are most often located in non-pigmented skin near mucocutaneous junctions such as on the eyelids, around the nostrils, lips, vulva, prepuce, penis or anus. The tumors are raised, fleshy, often ulcerated or infected and may have an irregular surface (Valentine, 2006). Rarely, primary SCC develops in the esophagus, stomach (non-glandular portion), nasal passages and sinuses, the hard palate, gums, guttural pouches and lung. The eyelid is the most common site, accounting for 40-50% of cases, followed by male (25-10% of cases) and female (10% of cases) genitalia (Knottenbelt, 2003).

Horses with lightly pigmented skin, such as those with a gray hair coat or white faces, are especially prone to developing SCC (Hewes & Sullins, 2009), and some breeds, such as Clydesdales, may have a genetic predisposition (Baker & Leyland, 1975). Exposure of light-colored skin to UV light has often been cited as a predisposing factor, but lesions can occur in dark skin and in areas that are not usually exposed to sunlight, such as around the anus. Exposure buildup of smegma ("the bean" in horseman's terms) on the penis is also linked to SCC (Taylor & Haldorson, 2013a) and is thought to be a carcinogen through penile irritation. Pony geldings and work horses are more prone to developing SCC on the penis, due to less frequent penile washing when compared to stallions (Haspeslagh, Vlaminck, & Martens, 2016).

Penile and preputial lesions are more likely with excessive smegma, persistent paraphimosis, or repeated trauma. Burn scars and chronic non-healing wounds may also be predisposed to SCC. Lesions are often solitary and can be erosive or productive. Nodular masses with seemingly intact skin may appear early followed by ulceration and/or necrosis. Some lesions gradually expand to develop a craterlike appearance or an expansive papillary mass may occur (Hewes & Sullins, 2009). Early lesions around the eye and on the penis are white raised plaques. Of SCC, 18.6% metastasize (Taylor & Haldorson, 2013a).

Histologically, SCC has irregular masses or cords of keratinocytes that invade the dermis and beyond. Focal areas of keratin surrounded by tumor cells (keratin pearls) and inflammation are defining features. Presumptive diagnosis of SCC may be reached based on lesion location and appearance, but histological confirmation is required (Hewes & Sullins, 2009). Small tumors found early in the disease process (most frequently on the eyelid) can be treated with cisplatin or radiation with favorable results. For more advanced cases, surgical removal of eye (enucleation), mass or penile amputation can be curative provided all tumours cells are removed (wide margins obtained) and there is no metastasis (Knottenbelt, 2003). However, young horses (usually geldings less than 8-years-old) that have a hard or "wooden" texture to SCCs on the glans penis have a very poor prognosis for treatment and recovery (Haspeslagh et al., 2016; Hewes & Sullins, 2009). Regular washing of the penis and prepuce in males as well as cleaning the clitoral fossa (the groove around the clitoris) in mares is recommended to remove smegma buildup, which also gives the opportunity for inspection for suspicious growths on the penis or on the vulva. The tumor is ulcerated and has multiple necrotic areas (black spots) (Figure 2, A) and Smooth, raised plaque on upper eyelid of a Paint horse (Figure 3, B).

Fig. 4: (A). SCC on the vulva of gray horse (B). SCC on upper eyelid of a Paint horse
Source: (Hewes & Sullins, 2009)

2.3. Equine Melanoma

Melanomas are masses that arise from melanocytes, dendritic cells of neuroectodermal origin, or melanoblasts. The third most common skin tumor in horses, melanomas are common in aging grey horses with Arabians, Thoroughbreds, Percherons, and dappled horses that undergo depigmentation being predisposed (Hewes & Sullins, 2009). Up to 15% of all equine skin tumors are melanocytic. More than 90% of these tumors are benign at initial presentation, but approximately two-thirds are thought to progress to malignancy and are capable of widespread metastasis. The vast majority appear in gray or white horses, usually at or before the age of 5 years, corresponding to the time in their life when their coat color changes (MacGillivray, Sweeney, & Piero, 2002; Valentine, 2006).

An early theory of equine melanocytic tumors suggested that dermal and visceral melanocytic tumors are a manifestation of a storage disease, rather than malignant neoplasia, and occur as a result of the accumulation of melanin in melanophages during the depigmentation process (Valentine, 2006). The prevalence of melanoma in gray horses over 15 years old has been estimated at 80%. One survey of Camargue-type horses found an overall population prevalence of 31.4%, with prevalence increasing to 67% in horses over 15 years old. Up to 66% of melanomas in gray horses are benign, but melanotic tumors in horses with darker hair-coats may be more aggressive and are more often malignant (MacGillivray et al., 2002; Valentine, 2006). One retrospective study of cases sent to a referral hospital reported a 14% prevalence of metastatic melanoma within the study population. However, the actual prevalence of metastatic melanoma may be lower due to infrequent submission of melanotic tumors for diagnosis (Burden, 2011; MacGillivray et al., 2002).

The most common sites for melanotic tumors are on the under-side of the tail near the base, on the prepuce, around the mouth or in the skin over the parotid gland (near the base of the ear) will initially begin as single, small raised areas that may multiply or coalesce into multi-lobed masses (a process called melanomatosis) over time (Valentine, 2006). Horses under 2-years-old can be born with or acquire benign melanotic tumors (called melanocytomas), but these tumors are often located on the legs or trunk, not beneath the tail as in older animals (E. L. Brown et al., 2014; MacGillivray et al., 2002). Equine metanocytic tumors have traditionally been grouped according to one of the three growth patterns. Some grow slowly over many years without metastasizing, whereas others grow slowly initially, with a subsequent increase in the rate of growth after a few years. A third subset grows rapidly and is malignant from the beginning (Scott et al., 2001).

According to Valentine, equine melanoma has at least four possible syndromes where three of which have the potential for

metastatic behavior (Valentine, 2006). Two of these three categories, dermal melanoma and dermal melanomatosis, are histologically very similar and can only be classified based on clinical features. Dermal melanomas are usually solitary, discrete lesions that are surgically excisable, occurring in a wide age range of gray horses. Dermal melanomatosis denotes the presence of many lesions, often coalescing and usually occurring in typical locations, such as the genital or perineal region, of gray horses older than 15 years. These are not surgically curable and are much more likely to metastasize internally (Scott et al., 2001; Smith, Goldschmidt, & McManus, 2002).

The third category refers to anaplastic melanoma in aged, non-gray horses. Although rare, it is the most aggressive, leading to death within months of diagnosis. The fourth category is the melanocytic nevi, which are benign, pigmented lesions predominantly occurring in horses less than 6 years old (Valentine, 2006). Histopathologically, melanomas have atypical melanocytes in sheets, nests, or cords, and they have a close association with epitricial sweat glands and hair follicles (Hewes & Sullins, 2009).

The initial definitive diagnosis of melanoma is usually done by histopathologic evaluation, with cytopathology used as a screen before biopsy or as an adjunct to biopsy or other diagnostic modalities. On the other hand, cytopathology is used more frequently than biopsies for monitoring of metastasis in both human patients and animals. Although there are few large-scale studies in veterinary literature regarding specificity and sensitivity of fine needle aspiration cytology (FNAC) for detection of metastatic neoplasia, it is in common use, particularly for melanoma, carcinomas, and mast cell tumors (Langenbach, McManus, Hendrick, Shofer, & Sorenmo, 2001).

There are currently no reliable and consistent therapeutic options available for the treatment of equine melanoma (Brown et al., 2014). Surgical excision is considered the best clinical option. However, excision of melanoma is rarely curative because of difficulties in achieving a good surgical margin, inability to access the tumors surgically, and rapid recurrence of the disease near the surgical site due to the presence of abnormal melanoblasts (Burden, 2011). In addition, other treatment options such as chemotherapy (cisplatin) and radiation therapy, which are commonly practiced in other species, are of minimal benefit to horses with melanoma (Brown et al., 2014). Immunotherapies, especially therapeutic vaccination therapies, offer an additional treatment modality for equine melanoma patients (Müller et al., 2011).

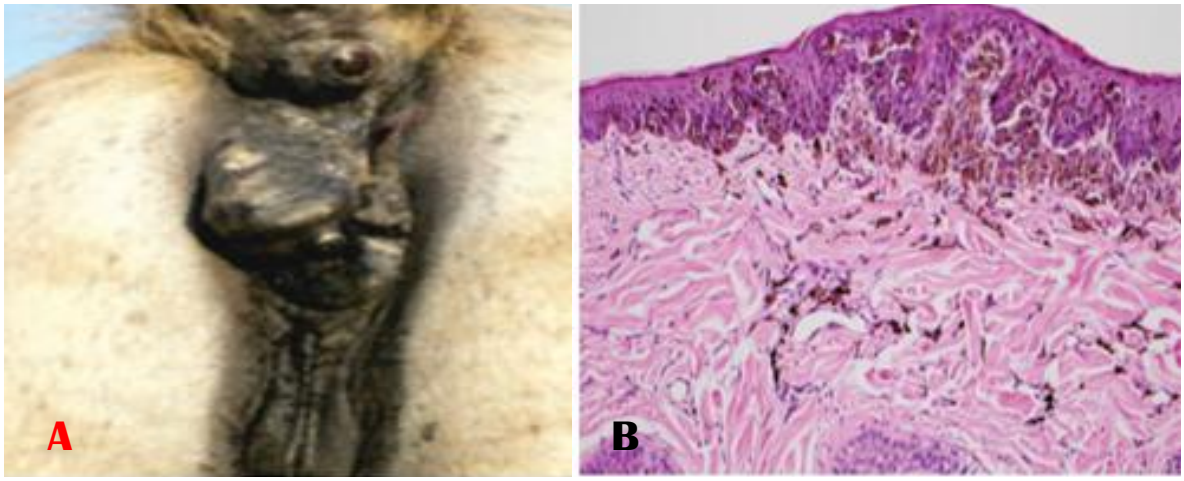

Fig. 3: Equine melanoma A) Melanocytoma, equine B) Melanocytoma, canine. compound melanocyte with intraepidermal and dermal proliferation of neoplastic melanocyte (Hewes & Sullins, 2009)

2.4. Equine Lymphoma or Lymphosarcoma

Lymphoma, also known as lymphosarcoma or malignant lymphoma is a haematopoietic tumor arising from lymphoid tissue that includes lymph nodes, spleen and gut associated lymphoid tissue. It was first reported in a horse in 1858 and is now the most commonly diagnosed haematopoietic tumor in horses worldwide (Taintor & Schleis, 2011). The overall incidence of lymphoma is approximately 1.3-2.8% of all equine tumours and has a prevalence of 0.002-0.5% in the equine population. There is no breed or sex predilection and any age of horse can be affected, but a majority of reported cases are in horses' age 4-10 years old. No specific risk factors have been identified and, although there appears to be no genetic predisposition for the development of lymphoma (Knottenbelt, 2003; Taintor & Schleis, 2011).

Equine lymphoma is classified into the following clinical syndromes: multicentric or generalised, alimentary, mediastinal, cutaneous and solitary tumours of extranodal sites. Although clinical signs reflect the function of the organ involved and the degree and duration of involvement, common clinical signs for all forms of equine lymphoma include weight loss, depression, lethargy, oedema of the ventral portion of the body wall or distal limb, recurrent fever and lymphadenopathy if peripheral lymph nodes are involved (Dorn et al., 1971; Knottenbelt, 2003; Meyer, Delay, & Bienzle, 2006).

Multicentric lymphoma, the most common form of equine lymphoma, is characterised by widespread involvement of lymph nodes, peripheral and/or internal, and a variety of organs most likely through distribution of neoplastic lymphocytes via lymphatic circulation (Knottenbelt, 2003; Meyer et al., 2006). Liver, spleen, intestine, kidney and bone marrow (leukaemic lymphoma) are the organs most commonly affected, but lymphoma of the upper airway, central nervous system, heart, adrenal glands, reproductive organs and eye have also been reported (Taintor & Schleis, 2011).

Approximately 19% of all horses with lymphoma have the alimentary form and, unlike the mean reported age for horses with lymphoma, this type of lymphoma was observed in older horses (mean age of 16 years). The small intestine was more commonly involved than the large intestine, but multiple segments of both small and large intestine also can be affected and lead to involvement of other organs and/or lymph nodes which often makes alimentary lymphoma difficult to differentiate from the multicentric form. Alimentary lymphoma is likely to affect multiple segments of intestine in young horses (<10 years) while focal intestinal lesions are often more likely to occur in older horses (Knottenbelt, 2003; Meyer et al., 2006; Taintor & Schleis, 2011).

Mediastinal lymphoma, also known as thoracic or thymic lymphoma, is the most common neoplasm of the thorax and has been found in horses of all ages. Besides the common clinical signs encountered with all lymphomas, horses with mediastinal lymphoma may also have dyspnoea, coughing and distension of the jugular vein (Taintor & Schleis, 2011). Cutaneous lymphomas are characterized by multifocal, subcutaneous nodules that may become alopecic, ulcerated and exude a yellow-coloured fluid and its common locations are the head, limbs, trunk and perineum (De Bruijn et al., 2007; Jacobs, Messick, & Valli, 2002).

Histological characteristics of lymphoma that distinguish it from lymphoid hyperplasia include compression or destruction of normal tissue architecture, a single population of cells with unorganized chromatin pattern, and variably sized and shaped nucleoli and parafollicular atrophy (Taintor & Schleis, 2011). Fine-needle aspiration or biopsy (incisional or excisional) of suspected lesions is the preferred method for diagnosis of lymphoma. Tissue samples allow for not only histological diagnosis but also for categorizing the lymphoma into B or T cell origin, determining the proliferation rate

and presence of hormone receptors (De Bruijn et al., 2007; Meyer et al., 2006).

Currently, a histological diagnosis of equine lymphoma is usually the end of an investigation, but further classification, as is done in human oncology, might allow for a more refined prognosis, strategic therapy and therapeutic monitoring. Staging the disease may aid in determining what treatment options, if any, may be available (Taintor & Schleis, 2011). WHO has developed a clinical staging system for lymphoma in domestic animals based on anatomic site and extent of organ involvement and clinical signs (De Bruijn et al., 2007; Meyer et al., 2006).

Based on clinical stage, options available include surgical excision of solitary tumours, radiotherapy and chemotherapy. However, it is important to remind the owner that therapy is unlikely to be curative but only palliative. There are several reports describing outcome of horses undergoing surgical excision or reduction of solitary masses of lymphoma involving the large colon, eye and upper airway in the horse (Burba, Jann, & Confer, 1991; Dabareiner, Sullins, & Goodrich, 1996).

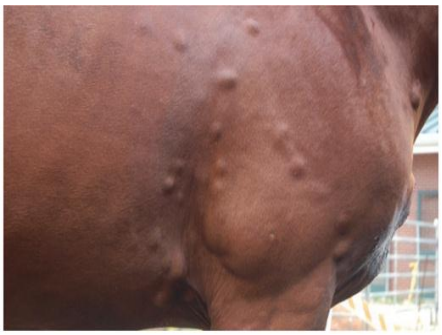

Figure 4: Cutaneous lymphoma
Source: (Taintor & Schleis, 2011)

3. COMMON SKIN TUMORS IN RUMINANTS

3.1. Melanoma

Melanomas originate from neuroectodermal melanoblasts, which migrate at the beginning of the development period into the epidermal-dermal junction of the skin, follicles, and dermis. They are also found in ocular structures, meninges, adrenal glands, endocardium, and intima of blood vessels (Brito et al., 2009; Burden, 2011). Melanoma in cattle, sheep and goats has been less studied, probably due to the low incidence of this tumor in ruminants. Cattle melanomas represent about 5% of the cases of tumors found in this species, and of all cases, 92% are benign (Cotchin, 1960; Miller et al., 1995). These tumors are common in dogs and in gray or white horses, and they are less frequent in cats and sheep (Godoy et al., 2003).

Although the congenital form is well known, melanomas are also common in Suffolk sheep and Angora goats of different ages and usually account for 5% to 6% of all tumors in this species especially in the Aberdeen Angus breeds (Miller et al., 1995; Smith et al., 2002). Some melanocytic tumors are congenital (Miller et al., 1995) or occur in cattle younger than two years old especially those of red, gray or black skin (Brito et al., 2009). The tumors may also be found on the jaw (Head, Else, & Dubielzig, 2002) maxilla (Brito et al., 2009), trunk, limbs (Miller et al., 1995) and less frequently in the interdigital regions (Godoy et al., 2003) and in the eyes (Brito et al., 2009).

Melanomas in the vertical branch of the jaw have been described in a 14-month-old Charolais and a 9-month-old Ayrshire and were already present at birth in the latter. Although the origin and pathogenesis of cutaneous melanomas are still unknown in animals, there is some evidence that the majority arise from epidermal, dermal, ocular and oral epithelia (Conroy, 1967). It is claimed that the majority of melanoma of Angora goat is caused by secondary mutations due to ultra-violet radiation (Brito et al., 2009).

According to the predominant cell type, melanomas are classified as epithelioid, spindle cell melanomas, mixed (M. H. Goldschmidt, 1998) and whorled or dendritic melanomas (Smith et al., 2002). Histologically the tumor was composed of heavily pigmented spindle-shaped cells with a highly angular shape or stellate, sometimes with long cytoplasmic processes, arranged in sheets in a

band-like pattern and sometimes whorled (Goldschmidt & Hendrick, 2002; M. H. Goldschmidt, 1998).

Most cells had small, round to oval nuclei containing 1-2 round nucleoli with delicate chromatin and abundant granular black pigment in the cytoplasm, in which the pigment darkened the cellular details. There were also strikingly large, polyhedral or round, well-delimited pigment-containing melanophages, which were more abundant than dendritic cells and were distributed throughout the tumor. Stromal collagen was minimal, and mitoses were absent or sparsely visible. Junctional activity was not observed. There was a low nucleus to cytoplasm ratio. Anisocytosis, anisokaryosis, and atypia were discrete. Tumor cells infiltrated the tongue, salivary glands, gums and lips. Bone invasion and jawbone osteolysis were observed (Brito et al., 2009; Smith et al., 2002). Excision is curative for most; however, rare malignant variants have been recognized with distant metastasis (Villalobos, 2011).

3.2. Bovine Lymphosarcoma

Lymphosarcoma has been described as the most common tumor in cattle, from 3-6 years of age. Lymphosarcoma in cattle may be sporadic which is seen in calves and young stock and has no known cause or result from infection with bovine leukemia virus (BLV) often referred to as an enzootic bovine leukosis which is seen in adults. Sporadic bovine leucosis occurs in three forms; juvenile, thymic and skin forms. Sporadic bovine leucosis (lymphosarcoma) rarely affects cattle older than two years of age (Angel, Stott, Tyler, & Groth, 1991; Misdorp, 2002).

Juvenile lymphosarcoma occurs most often in animals less than 6-month-old, thymic lymphosarcoma affects cattle 6-24 months old, and cutaneous lymphosarcoma is most common in cattle 1-3 yr old. Cutaneous lymphosarcoma presents as cutaneous plaques, 1-5 cm in diameter, on the neck, back, rump, and thighs. Regional lymph nodes may also be enlarged. This form of lymphosarcoma may undergo spontaneous remission; however, relapses may occur (Nagy, 2006; Ott, Johnson, & Wells, 2003).

Lymphosarcoma may appear as yellow-tan, discrete nodular masses or a diffuse tissue infiltrate. The latter pattern results in an enlarged, pale organ and can be easily misinterpreted as a degenerative change rather than a tumor (Angel et al., 1991; Gnad, Sargeant, Chenoweth, & Walz, 2004). Animals with BLV-associated lymphosarcoma commonly show lesions in the central or peripheral lymph nodes, leading to lymphadenopathy (Nagy, 2006). Histologically, the tumor masses are composed of densely packed, monomorphic lymphocytic cells (Angel et al., 1991; Gnad et al., 2004). The diagnosis of lymphosarcoma must be made by cytology or histopathology. Cytologic diagnosis is sometimes difficult because of the frequency of blood contamination of the aspirates. There is no treatment for viral infection or for lymphosarcoma in cattle. Eradication programs have been developed but success has been variable (Nagy, 2006; Ott et al., 2003).

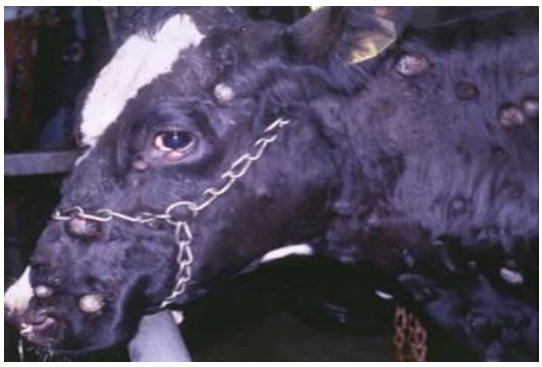

Fig. 5: Cutaneous lymphosarcoma
Source: (Nagy, 2006).

3.3. Papillomatosis (Warts, Fibropapillomas)

This is a benign, exophytic proliferation of the epidermis, and is common in the horse and in cattle, uncommon in the dog, cat, sheep, and goat. In most species, except the goat, young animals are preferentially affected; in goats, adult females are most commonly affected. There are several reports of congenital papillomas in a calf (Desrochers, St-Jean, &

Kennedy, 1994; Goldschmidt & Hendrick, 2002).

It is caused by bovine papillomavirus of which there are 6 subtypes described which can be associated with different forms of papillomas and classified into two subgroups, A and B. Subgroup A (BPV-1, BPV-2, BPV-5) will induce fibropapillomas with involvement of dermal fibroblasts and keratinocytes, and subgroup B will induce epithelial papillomas (BPV-3, BPV-6) with only keratinocyte involvement. BPV-4 infects the mucosal epithelium of the upper alimentary canal and induces pure epithelial papillomas (Campo & Roden, 2010).

In cattle, papilloma and fibropapilloma are usually located in the head, neck, shoulders, neck folds, limbs and udder. Tumor formations are multiple; they can be generalized in almost all body areas, having a typical papilloma appearance of variable sizes, from 1-2 cm upto large structures, which are rough, dense, and cauliflower-like. Tumors are exophytic, sometimes with a large attachment base or pediculate (Constable et al., 2016).

Papillomatosis in sheep and goats develops with locations in different body areas. In sheep, primary tumors occur in the head and ears, as papillomas and fibropapillomas, squamous cells become hypertrophied, forming horny skin plaques (Constable et al., 2016). In goats, tumors appear both in pigmented and non-pigmented skin areas. They can be located in the head, neck, trunk and mammary gland, usually a multicentric form. In this species, viral etiology could not be demonstrated, but the action of solar rays seems to favor and/or induce proliferation. Clinical and epidemiological data demonstrate the evolution of papillomas and fibropapillomas into squamous cell carcinoma (Goldschmidt & Hendrick, 2002; Meuten, 2016).

Histopathologic features of cutaneous papillomas were subdivided into the naturally developing lesions into three phases: a growing phase, a developing phase, and a regressing phase. The growing phase was characterized by basal cell hyperplasia, mild to moderate acanthosis, hyperkeratosis and parakeratosis, and a few intranuclear inclusion bodies. The developing phase was characterized by marked acanthosis with cell swelling and marked hyperkeratosis and parakeratosis. Many intranuclear inclusion bodies were present in swollen or degenerating cells of the upper spinous and granular cell layers. The regressing phase was characterized by slight epidermal hyperplasia, accentuation of the rete, moderate proliferation of fibroblasts, and collagen deposition along with an infiltrate of T lymphocytes at the epidermal-dermal interface (Goldschmidt & Hendrick, 2008; Meuten, 2016).

Diagnosis in the case of papilloma or fibropapilloma is relatively easy to make, considering the somewhat specific locations for the different animals; in dogs, oral papillomas require differential diagnosis from melanotic nodules, by histological examination (Goldschmidt & Hendrick, 2002). Treatment, for all species, will be surgical or electrosurgical, usually with good results. The possibility of the spontaneous disappearance of papillomas is considered. Vaccinations have very good results and autovaccination is recommended especially for cattle, dogs, and horses. Autohemotherapy, in cattle with cutaneous papillomas, has promising results, the success rate is 70% in cows treated with 30 ml blood harvested and immediately inoculated subcutaneously, 3-4 injections at 7-10-day intervals (Goldschmidt & Hendrick, 2008; Meuten, 2016).

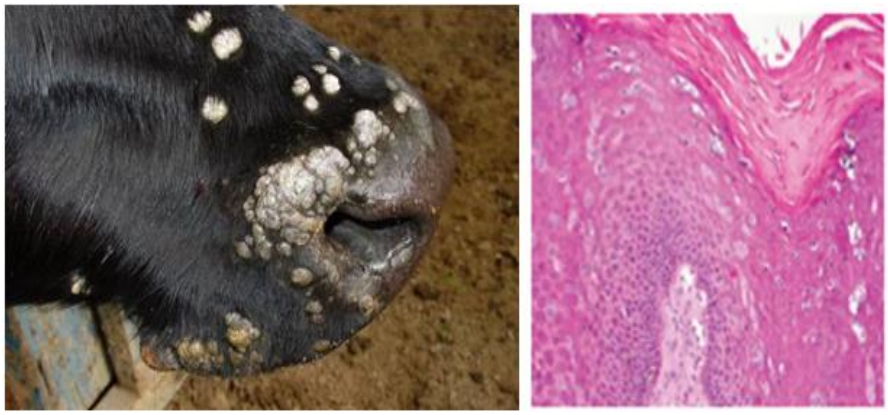

Fig. 6: Papilloma
Source (Constable et al., 2016)

3.4. Ocular Squamous Cell Carcinoma (Cancer Eye)

This is a malignant tumor of epidermal cells in which the cells show differentiation to keratinocytes (Goldschmidt & Hendrick, 2008). These tumors are commonly reported affecting older beef cattle in many subtropical countries, following prolonged exposure to ultraviolet light, lack of pigment within the epidermis at the sites of tumor development, and lack of hair or a very sparse hair coat at the affected sites (Goldschmidt & Hendrick, 2008; Hargis et al., 1977).

In cattle, these tumors are most common in breeds with white hair and poorly pigmented skin (especially Holsteins and Ayrshires) and, as in horses, develop around the mucous membranes, usually at the mucocutaneous junctions, particularly the periocular and vulvar regions. In India, squamous cell carcinomas of the horn core are common in aged bullocks. The most common cause is actinic injury. Solar keratoses often precede the development of an invasive tumor; genetic factors, immunodeficiency, and viruses may also play a role (Hargis et al., 1977).

In sheep, squamous cell carcinomas are of economic significance in some parts of the world. The Merino breed is most at risk, and females more so than males. The most common sites are the poorly haired skin of the ears, lips, muzzle, and the vulvar lips after they have been externalized by a Mules operation to prevent flystrike. Tumors at these sites develop in conjunction with solar injury, which is heightened when animals ingest photosensitizing plants. Tumors of the ears also develop more frequently after a procedure such as ear tagging. Squamous cell carcinomas can develop from follicular cysts on sites not commonly exposed to sunlight (Goldschmidt & Hendrick, 2002; Hargis et al., 1977).

In goats, squamous cell carcinomas develop most frequently in females, in which tumors develop on the perineal and vulvar regions and on the skin of the teats and udders. Both males and females can develop sun-induced tumors on the ears. Although Angoras are most at risk, Saanen goats occasionally develop squamous cell carcinomas on the udder in association with papillomas (Goldschmidt & Hendrick, 2008).

Actinic keratosis (squamous cell carcinoma) shows epidermal hyperplasia, hyperkeratosis, parakeratosis, acanthosis, accentuation of the epidermal rete, and keratinocyte dysplasia (Goldschmidt & Hendrick, 2002; Hargis et al., 1977). The affected keratinocytes, which are mostly found in the basal and spinous layer, show loss of polarity, karyomegaly, nuclear hyperchromatism, enlarged and prominent nucleoli, and mitotic figures of basal and suprabasal keratinocytes. Because this lesion is induced by prolonged ultraviolet light exposure, some cases may show solar elastosis, (Campbell, Gross, & Adams, 1987) with degeneration and fragmentation of elastic and collagen fibers in the superficial dermis and deposition of thickened, basophilic fibrillar material that stains positive with the van Gieson elastin stain. At this stage there is

no invasion through the basement membrane by the dysplastic keratinocytes, such as occurs with squamous cell carcinoma, extending into the dermis, with or without an association to the overlying epidermis, are islands, cords, and trabeculae of neoplastic epithelial cells showing a variable degree of squamous differentiation (Goldschmidt & Hendrick, 2002; Hargis et al., 1977).

The amount of keratin, seen as intracytoplasmic, eosinophilic fibrillar material (keratin tonofibers), produced by the neoplastic cells is quite variable; there is extensive keratinization, and in well-differentiated tumors, there is formation of distinct keratin "pearls". In poorly differentiated tumors only a few cells have intracytoplasmic eosinophilic keratin tonofibers. Individual tumor cells have large, ovoid, often vesicular nuclei with a single, central, prominent nucleolus, abundant cytoplasm that varies from pale to brightly eosinophilic, and distinct cell borders. In more differentiated tumors it is also possible to recognize intercellular desmosomes, especially in areas where intercellular edema allows them to be more readily identified (Campbell et al., 1987).

The number of mitotic figures is variable, but they are more frequent in less well-differentiated tumors. Invasion of the dermis and subcutaneous tissue may evoke a desmoplastic response. Ulceration is accompanied by an infiltrate of neutrophils into the superficial part of the tumor, while plasma cells and lymphocytes are found in the deeper parts of the tumor. The invasive margins of the tumor may show neurotropism as well as invasion of dermal and subcutaneous lymphatics (Goldschmidt & Hendrick, 2008).

Several uncommon variants of squamous cell carcinoma have been described. The spindle cell variant of squamous cell carcinoma is often difficult to differentiate from the surrounding stromal cells. However, the tumor cells stain positive with antikeratin antibodies on immunohistochemical evaluation. Acantholytic squamous cell carcinomas are characterized by marked adhesion of the neoplastic cells, which results in a pseudo glandular pattern (the basal neoplastic cells have remained attached to the basal lamina), but there is individualization of the neoplastic keratinocytes that make up the centers of the islands of neoplastic squamous cells (Goldschmidt & Hendrick, 2008; Hargis et al., 1977). Invasive squamous cell carcinomas in Beagles at the site of prior vaccination with an autogenous papillomavirus vaccine will show positive staining of nuclei in the granular cell layer on immunohistochemical examination for the canine papillomavirus (Bregman, Hirth, Sundberg, & Christensen, 1987).

The gold standard for the diagnosis of squamous cell carcinoma is the histopathological evaluation of the lesion after an incisional or excisional biopsy, and also it is diagnosed based on the presence of the universal cytological criteria which included nuclear enlargement, hyperchromasia, irregular nuclear outline, coarse nuclear chromatin, and prominent nucleoli. Management modalities in OSSN range from complete excision in well-delineated tumors to chemotherapy in diffuse unresectable lesions (Mittal, Rath, & Vemuganti, 2013).

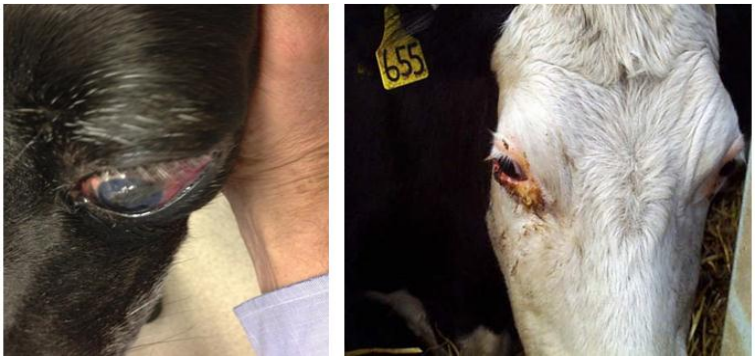

Fig. 7: Ocular squamous cell carcinoma (OSSN)
Source (Goldschmidt & Hendrick, 2008; Nagy, 2006).

4. SKIN TUMORS IN SMALL ANIMAL

Mammary gland tumors, skin tumors, osteosarcomas and hemopoietic tumors are among the commonest malignancies in dogs and cats. Among these, skin tumors are the most common tumors in dogs accounting for approximately 30% of all diagnosed tumors (Bonnett, Egenvall, Hedhammar, & Olson, 2005; Proschowsky, Rugbjerg, & Ersbøll, 2003). A number of endogenous factors-genetic, immune, and hormonal, are also important. The fact that tumor is more commonly observed in older patients supports the concept that, over the course of time, a combination of factors leads to a normal cell's transformation into a tumor cell. Each of these factors increases the likelihood of the appearance of a tumor, and they are therefore called risk factors (Proschowsky et al., 2003).

Dogs are affected by skin tumors 35 times more often than humans are. They are also affected 4 times more often by mammary gland tumors, 8 times more often by bone tumor, and twice more often by leukemia, than people do (Cullen, Page, & Misdorp, 2002). Around 35-45% of all tumors in cats are of the type that affects the skin and the soft tissues, while hemopoietic malignancies constitute 30-40% of the whole. Around 55% of skin tumors in dogs originate from the mesenchymal tissues, the other 45% from the epithelium (Priester, 1980). The commonest of the mesenchymal tumors in dogs are the histiocytomas, lipomas, fat tissue cells tumors, and the fibrosarcomas (Carpenter, Andrews, & Holzworth, 1987). In Siamese cats, fat tissue tumors are encountered three times as much as in other feline breeds (Miller et al., 1991). Of the epithelial skin tumors in dogs, the most prevalent are tumors in the fat tissue cells and papillomas, while in cats, the most prevalent are basal cell tumors, and squamous cell carcinomas (Carpenter et al., 1987; Miller et al., 1991).

4.1. Basal Cell Tumor

The basal cell carcinoma is one of the most frequent pigmented skin tumors in dogs and cats (Baba & Câtoi, 2007; Scott et al., 2001). There are a number of common synonyms for basal cell tumors including rodent ulcer, basal cell carcinoma, basosquamous carcinoma, basal cell epithelioma, and basaloma (Cotchin, 1960). Basal cell tumors originate from uncommitted basal reserve cells of the epidermis and adnexa and exhibit minimal differentiation toward hair follicle or other adnexa (Welle, Bley, Howard, & Rüfenacht, 2008).

In dogs, statistics indicate a rate of 3-5-10% of all tumors, and in cats a percentage of up to 18%. In terms of age, in both dogs and cats, the adult age, 7 years in dogs and 9 years in cats, has a higher incidence. Males are more frequently affected by basaliomas, compared to females, and the dog breeds that seem to be more sensitive are Cocker Spaniel and Caniche (Baba & Câtoi, 2007; Meuten, 2016).

Persian and older cats have a predisposition for basaliomas, presenting ulcerated plaques at the level of the head, extremities and neck. These malignant tumors have continuity with the epidermis, evolving with local invasion, but without metastases (M. H. Goldschmidt, 1998). In dogs, basal cell carcinomas histologically show cornification, being termed basosquamous carcinomas that are found in old Saint Bernard, Scottish terrier and Norwegian elkhound dog breeds. They may be located in any body area, under the form of endoexophytic nodules or plaques (Baba & Câtoi, 2007; M. H. Goldschmidt, 1998).

Histologically, basalioma cells are characterized by oval prominent nuclei and a small amount of cytoplasm; they generally have small sizes and are uniform. Basalioma cells are very similar to epidermal basal cells. The mitotic index, in the case of this tumor, is high. Basal cells frequently contain abundant melanin amounts, especially in cats, which is why they should not be confused with pigmented tumors (Goldschmidt *et al.*, 1998; Baba and Catoi, 2007).

In the dog, basal cell tumors have six major histologic patterns: solid, garland (ribbon), medusoid, adenoid, cystic, and basosquamous. The solid and baso-squamous varieties are believed to be more aggressive. It

has been noted that basal cell tumors of cats differ from those of the dog morphologically and in site incidence (Cotchin, 1960; Diters & Walsh, 1984).

Basal cell tumor is differentiated from basal cell carcinoma by the lack of invasion and associated fibroplasia at the periphery of the benign tumors. The treatment of choice is surgical excision. Incomplete excision may result in tumor recurrence. Fine needle aspiration cytology, whereby cells extracted from just under the skin for evaluation, may reveal round cells with dark blue cytoplasm. Occasionally, cells may even be dividing at an alarming rate, also known as a high mitotic rate. For definitive diagnosis, however, a diagnostic procedure known as histopathologic examination is needed. This will involve examining thin slices of the tumor under a microscope (Goldschmidt & Hendrick, 2008; M. H. Goldschmidt, 1998).

The best option for treatment depends on the type of tumor present, its size, and its location on the body. For most basal cell tumors, the treatment method with the best success is the surgical removal of the tumor followed by radiation and chemotherapy. These treatment options are usually paired with the surgical removal of a malignant basal cell tumor. Both of these options work to destroy cancer cells on a microscopic level. Cryosurgery is required if the tumor is small enough, it may be possible to freeze it off with liquid nitrogen (Meuten, 2016).

4.2. Squamous Cell Carcinoma

Squamous cell carcinoma, a malignant tumor of epidermal cells with varying degrees of keratinocyte (squamous cell) differentiation (Bussanich, 1987). Based on the location of the body, squamous cell carcinomas are classified as cutaneous squamous cell carcinoma (actinic keratosis) (tumors that occur in the skin especially hyperpigmented areas with a high rate of exposure to sunlight), subungual squamous cell carcinoma (tumor in the epithelial layer of the nail bed, this is the most common form of squamous cell carcinoma, accounting for about 50% of digital tumors in dogs) and Oral squamous cell carcinoma (occurs in the mouth, more common in older neutered females) (Coyle & Garrett, 2009).

In most of the cases of squamous cell carcinoma consist of islands, cords, and trabeculae of invasive epithelial cells that almost always have an association with the overlying epidermis, in which there has been a breaching of the basal lamina zone. There is often the formation of keratin pearls (concentric lamellae of keratin within the tumor) by invasive neoplastic cells. The cells and nuclei are large, nuclei are hyperchromatic, and chromatin often appears clumped. Nucleoli vary in size and may be prominent. Whereas those tumors that are well differentiated from keratin pearls, poorly differentiated tumors only show keratinization of individual cells (M. Goldschmidt, 1998; M. H. Goldschmidt, 1998).

This tumor is frequently associated with solar dermatosis, which is the tumor of the cells of the malpighian layer from the epidermis. It has a high incidence, being reported in all species of domestic animals, with a higher frequency in horses, dogs and cats, especially in adult and old animals. Although breed does not seem to be a risk factor, some authors report a higher sensitivity for Labrador and black Caniche dogs, with location in the digits, and for Dalmatian, Beagle, Whippets and white English Bull Terrier breeds, with location in the flank and the abdomen. Two uncommon histologic variants of squamous cell carcinoma occur: acantholytic squamous cell carcinoma, in which there has been dyshesion and degeneration of tumor cells resulting in cyst formation with a single peripheral layer of tumor cells, producing a pseudo glandular pattern; spindle cell squamous cell carcinoma, in which tumor cells are fusiform; cytokeratin stains are often positive and help to identify these rare tumors as squamous cell carcinoma (Bussanich, 1987; Goldschmidt & Hendrick, 2008).

Accurate diagnosis will be made with cytology to examine the sample of tumors for

this a biopsy or needle aspirant will be taken with a local anesthetic. In some cases, the veterinarian may decide to surgically remove the tumor first, and diagnose the tumor microscopically after removal (Coyle & Garrett, 2009). Surgical removal of the squamous cell carcinoma is the treatment of choice, but removal of the entire tumor may not always be possible because of its size or location. In this case, additional treatment may include Radiation therapy, Plesiotherapy, Cryotherapy Photodynamic therapy and Chemotherapy (Meuten, 2016).

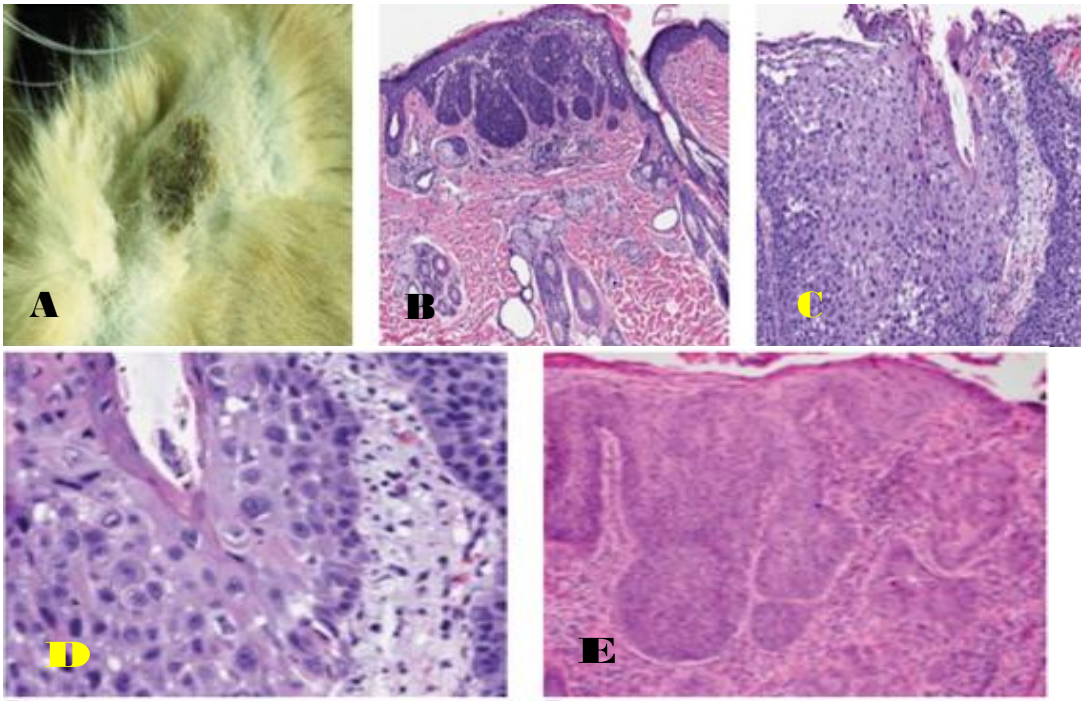

Fig. 8: Squamous cell carcinoma

A-E Feline squamous cell carcinoma in-situ (B) Proliferation of neoplastic keratinocytes within the epidermis and follicular infundibulum but without invasion through the basement membrane into the dermis (C) Disorganized keratinocytes within the epidermis and follicular infundibulum (D) Keratinocytes exhibiting viral cytopathic effects (E) Progression to invasive squamous cell carcinoma (Goldschmidt & Hendrick, 2008).

4.3. Mast Cell Tumor

Mast cell tumors (MCTs) are highly invasive and metastatic and are the most frequent round cell tumors in dogs, comprising 16-21% of all cutaneous tumors diagnosed and are the most common skin tumors in dogs, representing about 7% to 21% of all dog skin tumors and 11% to 27 % of malignant skin tumors in this species (Misdorp, 2004; Newman, Mrkonjich, Walker, & Rohrbach, 2007). Canine MCTs have variable biologic behaviors, ranging from solitary benign masses that can be cured with surgery alone to systemic and potentially fatal metastatic disease and are always considered potentially malignant, but their true metastatic potential is not entirely known (Welle et al., 2008).

Mast cell tumors in dogs can occur in two different forms: common as cutaneous tumor, or less common as a systemic form of tumors mast cell proliferation; systemic mastocytosis (Marinković et al., 2015). Boxers, Pugs, Boston terriers, Weimaraners, Labrador retrievers and Golden retrievers have a high propensity for cutaneous mast cell tumors (CMCT). Syst (Goldschmidt & Hendrick, 2008)emic mastocytosis (systemic mast cell tumor) is a term used to describe the proliferation and invasion of tumors mast cells in several tissues, such as subcutis, lymph nodes, internal organs and bone marrow, with

or without concurrent mast cell leukemia. This type of mast cell tumor is less frequent compared to cutaneous mast cell tumor, which represents one of the commonest skin tumors in dogs (Welle et al., 2008).

MCTs are most often graded histologically by the scheme described by (Patnaik, Ehler, & MacEwen, 1984), and nowadays more often by the grading system proposed by (Kiupel et al., 2011). Patnaik grading system is based on the level of differentiation, cellularity, cellular morphology, mitotic index and tissue reaction and it has been widely used (Hosseini et al., 2014). Tumors of grade I are circumscribed, mainly dermal in location, and consist of well-differentiated mast cells with prominent metachromatic cytoplasmic granules. Poor cellular differentiation, aggressive growth pattern, moderate to high mitotic activity, mitotic atypia and sparse to absent cytoplasmic granulation are the major features of grade III tumours. Grade II MCTs constitute an intermediary form between the two other grades, but they tend to infiltrate more deeply than grade I tumors (Patnaik et al., 1984).

According to the Kiupel grading system, high-grade MCTs include tumors with at least one of the following features: at least 7 mitotic figures in 10 high power fields (hpf); at least 3 multinucleated cells in 10 hpf; at least 3 bizarre nuclei in 10 hpf; or at least 10% karyomegalic neoplastic cells. All other tumors are considered low grade (Kiupel et al., 2011).

MCTs are routinely diagnosed by cytology and histopathology. Histopathologically, MCT tumor cells were less well-circumscribed by connective tissue and tumors cells often exhibited aggressive behavior, high cellularity, cellular pleomorphism, and various morphologic patterns. However, in some regions of the tumor tissue shows tumors cells extending into the subcutis. Tumor cells had distinct cell borders and widely variable amounts of pale to brightly eosinophilic cytoplasm. Furthermore, tumors had tumors cells containing numerous fine eosinophilic to basophilic cytoplasmic granules consistent with mast cell granules and also highly pleomorphic tumor cells with a high mitotic index, anisokaryosis and infiltration of the surrounding dermis and subcutis were observed (Hosseini et al., 2014).

Microscopical examination of the cytological smears obtained from all selected dogs (one with systemic mastocytosis and six with CMCT) revealed that the cellular specimen constituted mostly of round cells with central nuclei and fine to coarse purple cytoplasmic granules. A large number of eosinophils and degenerated neutrophils were also present in the cytological smears (Webster, Yuzbasiyan-Gurkan, Miller, Kaneene, & Kiupel, 2007). Most MCTs are easily diagnosed with fine-needle aspiration (FNA). Infrequently, MCT granules will not stain with Diff-Quik and need to be stained with a Wright's stain. On Diff-Quik cytology, if eosinophils are seen along with large round cells that lack granules, suspicion should be raised for an MCT and the slide submitted to a clinical pathology laboratory for a non-Diff-Quik stain (Withrow, Page, & Vail, 2013).

Surgical removal is the mainstay of the treatment of canine mast cell tumors. Because of their locally invasive behavior, wide margins of what appears to be normal tissue around the tumor needs to be removed to increase the likelihood that the tumor has been completely removed. For mast cell tumors that were not, or because of location, could not be completely removed, radiation therapy is often the best treatment for residual disease, although a more aggressive second surgery is possible for some dogs (Garrett, 2014; Krick, Billings, Shofer, Watanabe, & Sorenmo, 2009).

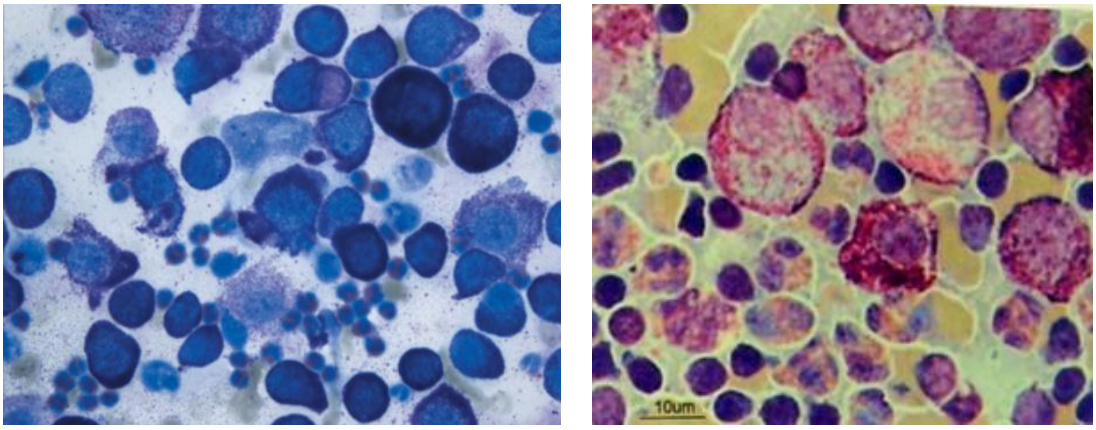

Fig. 9: Fine-needle aspirate smear of a mast cell tumor; note highly granular mast cells, staining is so intense that cellular morphology is often obscured.

Source (Welle et al., 2008)

4.4. Melanoma

Melanoma is a malignant tumor originating from melanocytes (Sweet et al., 2012). Canine malignant melanomas are located at different anatomical sites, such as the mouth, lips, skin, eyes, and digits. Studies are controversial about the most common location for this disease in dogs; however, most studies point to the oral cavity and skin as the most common sites (Curtin et al., 2005) in 40%-62% and 27%–31%, respectively (Teixeira et al., 2010; Gillard et al., 2014).

Several etiological factors are supposed to be involved in canine malignant melanomas, including consanguinity, trauma, chemical exposure, hormones, and genetic susceptibility. However, there is no consensus regarding the etiology of malignant melanomas in dogs (Smith et al., 2002). Sunlight may be involved in the development of this disease in the sun-exposed skin areas of the body, such as the face and pinnae; however, sunlight probably is not involved in mucosal melanomas, like the ones found in the canine buccal cavity. Other factors, like the presence of pigmented cells, trauma, chemical agents, or even the buccal microbiota, and inflammation may be associated with the etiology of these tumors (Dzutsev, Goldszmid, Viaud, Zitvogel, & Trinchieri, 2015).

There are four types of melanocytic tumors like melanocytic nevus, melanocytoma, malignant melanoma. Malignant melanoma can be further divided into Cutaneous Melanoma, Oral Melanoma, Uveal or Intra-ocular Melanoma and Limbal (Epibulbar) Melanoma. Melanocytic nevus (non-malignant forms of tumor are often referred to as melanocytic nevus). A nevus cell is usually a changed melanocyte. It implies any congenital, melanin pigmented lesion. They are typically well defined, deeply pigmented, less than 2 cm in diameter dome-shaped, firm and broad-based. But they are mobile under underlying tissues (Goldschmidt & Hendrick, 2008; Meuten, 2016).

Melanocytoma is a benign tumor arising from the melanocytes in the epidermis, dermis, or adnexa (appendages of an organ), but primarily originates from the external root sheath of the hair follicle (Head et al., 2002). Melanocytes, which are dendritic cells derived from the neuroectoderm and melanoblasts of the neural crest, migrate during embryogenesis to the dermis and epidermis, mucous membranes, and eyes. These dendritic cells in melanoma development have demonstrated altered expression of cell to cell adhesion molecules (Scott et al., 2001; Smith et al., 2002).

The development of malignant melanoma is generally characterized by a series of transitions that are outlined in and arises from melanocytes that normally reside within the basal layer of epidermis (Chin, 2003). Malignant melanoma can be subdivided into three patterns on the basis of cell shape: epithelioid (round and polygonal cells),

spindle cell (tumor resembles fibroblasts) and mixed tumors (show both cell types) could have a genetic basis (Head et al., 2002).

Histologically, malignant melanoma can be the highly melanotic type or the highly anaplastic amelanotic type. Anaplastic melanocytes can be large with abundant cytoplasm with one or more oval or elongated nuclei, with obvious nucleoli. These are frequently characterized to form nests in the submucosa by a mixed structure of epithelial-like cells and fusiform cells and junctional infiltration between basal cells and in the submucosa (Head et al., 2002). The most prominent biological property of melanoma cells is the ability to produce melanin. The disruption of homeostasis of close association between melanocytes and basal keratinocytes may trigger a continuous proliferation of the melanocytes, which may lead to the development of malignant melanoma. Once malignant melanoma cells have escaped from the keratinocyte control, they become able to invade the tissue by the degradation of the extracellular matrix through the action of metalloproteinases (Simonetti et al., 2002).

In contrast to digital melanomas, cutaneous melanomas typically have benign behavior in dogs, with the exception of melanomas that develop on the mucocutaneous junctions (Spangler & Kass, 2006). They account for 0.8%-2% of all canine cutaneous tumors, and are more commonly seen in dogs with heavily pigmented skin. Predisposed breeds include Scottish Terrier, Poodle, Golden Retriever, Dachshund, Cocker Spaniel, Miniature Poodle, Chow, and Gordon Setter (Bregman et al., 1987; Withrow et al., 2013). Benign skin melanomas are usually solitary, small, pigmented, firm, and freely moveable over deeper structures. Malignant melanomas tend to be fast-growing tumors, and often are ulcerated, and pigmented (grey, brown, or black) (M. H. Goldschmidt, 1998). The most common sites for benign cutaneous melanomas are the face (near the eyelids), trunk, and extremities (Smith et al., 2002).

The histopathological diagnosis of melanoma may be difficult if the tumor does not contain melanin. Amelanotic malignant melanomas may represent one-third of all melanoma cases in dogs. Their histopathological aspect may resemble carcinomas, sarcomas, lymphomas, and osteogenic tumors. For this reason, the diagnosis of malignant melanoma should be made with the use of immunohistochemistry (Chenier & Dore, 1999; Ramos-Vara et al., 2000). Most dogs are cured with complete surgical excision or, if the entire tumor cannot be removed, then radiation therapy may be added to the treatment (Smedley et al., 2011; Spangler & Kass, 2006).

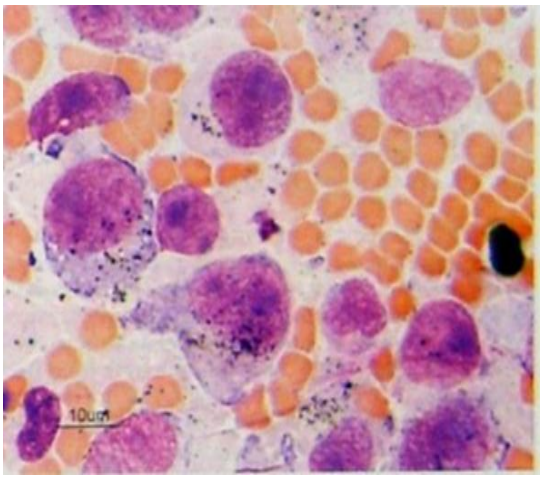

Fig. 10: Poorly pigmented Malignant Melanoma taken from oral cavity of dogs.
Source: (Cowell, Tyler, Meinkoth, & DeNicola, 2007)

4.5. Canine Transmissible Venereal Tumor

Canine transmissible venereal tumors (TVTs) are cauliflower-like, pedunculated, nodular, papillary, or multilobulated in appearance. TVTs may be solitary or multiple and are almost always located on the genitalia or, less commonly, on the lips or other portions of the skin or mucosa that come in contact with the genitalia (Goldschmidt & Hendrick, 2008). The transmission is usually during coitus and dogs of both sexes and all ages are affected, but the tumor is more commonly seen in female dogs that have reached sexual maturity. The distribution of transmissible venereal tumors (TVT) throughout the world is patchy and unexplained. The disease is enzootic in some regions of the Caribbean (e.g. Puerto

Rico), but it has never been reported in the British Isles. TVTs are seen frequently in portions of the Midwestern United States but are uncommon in the mid-Atlantic and relatively common in the southeastern states. It occurs in pockets in Europe, Africa, and Asia (Goldschmidt & Hendrick, 2008; Meuten, 2016).

TVTs vary in their gross appearance, but most are proliferative verrucous, papillary, or nodular masses protruding from the surface of the penis or vulva. The tumors can be small single nodules or multilobulated masses as large as 15cm in diameter. The surface is usually ulcerated and friable, with a smooth or granular appearance (N. Brown, Calvert, & MacEwen, 1980). The tumor is composed of loose sheets, rows and cords of relatively uniform round to ovoid cells. Cell margins are generally indistinct. Nuclei are large, round, with a single centrally placed nucleolus surrounded by marginated chromatin. There is a moderate amount of light pink to clear cytoplasm. The mitotic index is high. Variable numbers of lymphocytes, plasma cells and macrophages infiltrate the tumor. In regressing tumors, increased inflammation and zones of necrosis and fibrosis are often present (Goldschmidt & Hendrick, 2002).

Tumors grow rapidly at first and then remain static for a time, with eventual spontaneous regression after several months. Regression is the result of a humoral immune response (IgG) that makes the dog highly resistant to subsequent tumor implantation. There is infrequent metastasis to regional lymph nodes and, rarely, to viscera (Goldschmidt & Hendrick, 2002; Meuten, 2016). The diagnosis is based on the environmental history, clinical and cytological findings. Biopsy for histological examination is the most reliable method for diagnosis. If there is doubt about the histological diagnosis, a definitive diagnosis can be made by chromosome analysis and transmission studies. The ultimate goal of the treatment of the tumor is complete cure, which may be achieved by surgical excision, radiotherapy, immunotherapy and/or chemotherapy (Goldschmidt & Hendrick, 2002; Meuten, 2016).

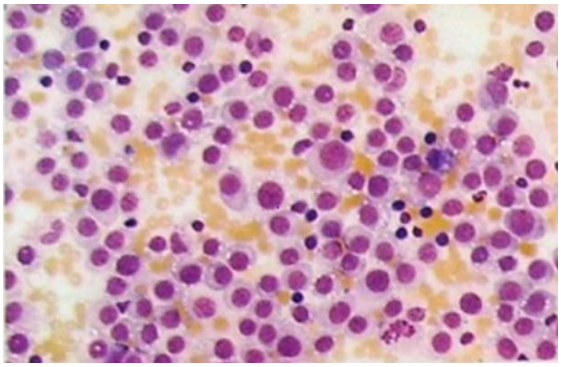

Fig. 5: Transmissible Venereal Tumor Source (Cowell et al., 2007)

CONCLUSION AND RECOMMENDATIONS

Tumors affecting the skin are the most commonly seen tumors in domestic animals. Common tumors that frequently occur on the skin of domestic animals include equine sarcoid, squamous cell carcinoma, lymphosarcoma, melanoma, basal cell tumor, papilloma, mastocytoma, and canine transmissible venereal tumor. Skin tumors are diagnosed more frequently than other tumors because of the fact that the skin is constantly exposed to many tumor-causing factors in the environment. It could be diagnosed through the use of histopathological and cytological techniques to reach on definitive diagnosis and for providing appropriate treatment. Hence, skin tumors are so diverse; the therapeutic approach has got certain restriction and need thorough identification by the veterinarian. In conclusion, the main skin and other tumors of domestic animals should be studied and complied comprehensively in single document. Accordingly, skin lesions should be carefully diagnosed based on clinical signs, cytology, and histopathology. Besides, facilities for Immunohistochemistry, radiology, and ultrasound should be fulfilled at least in veterinary university hospitals and clinics to diagnose tumors of domestic animals

REFERENCES

Angel, K., Stott, J., Tyler, J., & Groth, J. A. (1991). Metastatic thymic

lymphosarcoma in a calf. *Journal of the American Veterinary Medical Association, 198*(10), 1771-1773.

Baba, A. I., & Câtoi, C. (2007). Epithelial and melanocytic tumors of the skin *Comparative Oncology*: The Publishing House of the Romanian Academy.

Baker, J., & Leyland, A. (1975). Histological survey of tumours of the horse, with particular reference to those ofthe skin. *The Veterinary Record, 96*(19), 419-422.

Birbrair, A., Zhang, T., Wang, Z.-M., Messi, M. L., Olson, J. D., Mintz, A., & Delbono, O. (2014). Type-2 pericytes participate in normal and tumoral angiogenesis. *American Journal of Physiology-Cell Physiology, 307*(1), C25-C38.

Bonnett, B., Egenvall, A., Hedhammar, Å., & Olson, P. (2005). Mortality in over 350,000 insured Swedish dogs from 1995–2000: I. Breed-, gender-, age-and cause-specific rates. *Acta veterinaria scandinavica, 46*(3), 105.

Bregman, C., Hirth, R., Sundberg, J., & Christensen, E. (1987). Cutaneous neoplasms in dogs associated with canine oral papillomavirus vaccine. *Veterinary Pathology, 24*(6), 477-487.

Brito, M. d. F., França, T. N., Jabour, F. F., Seixas, J. N., Andrade, G. B., Oliveira, L. I., & Peixoto, P. V. (2009). Metastasizing oral melanoma in a cow. *Ciencia Rural, 39*(4), 1236-1240.

Brown, E. L., Ramiya, V. K., Wright, C. A., Jerald, M. M., Via, A. D., Kuppala, V. N., . . . Lawman, M. J. (2014). Treatment of metastatic equine melanoma with a plasmid DNA vaccine encoding Streptococcus pyogenes EMM55 protein. *Journal of Equine Veterinary Science, 34*(5), 704-708.

Brown, N., Calvert, C., & MacEwen, E. (1980). Chemotherapeutic management of transmissible venereal tumors in 30 dogs. *Journal of the American Veterinary Medical Association, 176*(10 Pt 1), 983-986.

Burba, D., Jann, H., & Confer, A. (1991). Surgical reduction of a laryngeal lymphosarcoma mass causing dyspnea in a horse. *Equine practice (USA)*.

Burden, K. (2011). Melanomas and their effect on the grey horse. *Young Scientists Journal, 4*(10), 75.

Burdin, M. (1964). Squamous-cell carcinoma of the vulva of cattle in Kenya. *Research in veterinary science, 5*(4), 497-509.

Bussanich, N. (1987). Canine uveal melanoma: Series and literature review. *J Am Anim Hosp Assoc, 23*, 415-422.

Campbell, G., Gross, T., & Adams, R. (1987). Solar elastosis with squamous cell carcinoma in two horses. *Veterinary Pathology, 24*(5), 463-464.

Campo, M. S., & Roden, R. B. (2010). Papillomavirus prophylactic vaccines: established successes, new approaches. *Journal of virology, 84*(3), 1214-1220.

Carpenter, J. L., Andrews, L. K., & Holzworth, J. (1987). Tumors and tumor-like lesions. *Diseases of the cat: medicine and surgery, 1*, 506-507.

Chenier, S., & Dore, M. (1999). Oral malignant melanoma with osteoid formation in a dog. *Veterinary Pathology, 36*(1), 74-76.

Chin, L. (2003). The genetics of malignant melanoma: lessons from mouse and man. *Nature Reviews Cancer, 3*(8), 559-570.

Conroy, J. D. (1967). Melanocytic tumors of domestic animals: With special reference to dogs. *Archives of dermatology, 96*(4), 372-380.

Constable, P. D., Hinchcliff, K. W., Done, S. H., & Grünberg, W. (2016). *Veterinary medicine-e-book: a textbook of the diseases of cattle, horses, sheep, pigs and goats*: Elsevier Health Sciences.

Cotchin, E. (1960). Tumours of farm animals: A survey of tumours examined at the Royal Veterinary College, London,

during 1950-60. *Veterinary Record, 72*, 816-823.

Cotchin, E. (1977). A general survey of tumours in the horse. *Equine veterinary journal, 9*(1), 16-21.

Cowell, R. L., Tyler, R. D., Meinkoth, J. H., & DeNicola, D. B. (2007). *Diagnostic cytology and hematology of the dog and cat-e-book*: Elsevier Health Sciences.

Coyle, V. J., & Garrett, L. D. (2009). Finding and treating oral melanoma, squamous cell carcinoma, and fibrosarcoma in dogs. *Veterinary medicine, 104*(6), 294-304.

Cullen, J., Page, R., & Misdorp, W. (2002). An overview of cancer pathogenesis, diagnosis, and management. *Tumors in domestic animals*, 1-44.

Cunningham, F., Fiebelkorn, S., Johnson, M., & Meredith, C. (2011). A novel application of the Margin of Exposure approach: Segregation of tobacco smoke toxicants. *Food and Chemical Toxicology, 49*(11), 2921-2933.

Curtin, J. A., Fridlyand, J., Kageshita, T., Patel, H. N., Busam, K. J., Kutzner, H., . . . LeBoit, P. E. (2005). Distinct sets of genetic alterations in melanoma. *New England Journal of Medicine, 353*(20), 2135-2147.

Dabareiner, R., Sullins, K., & Goodrich, L. (1996). Large colon resection for treatment of lymphosarcoma in two horses. *Journal of the American Veterinary Medical Association, 208*(6), 895-897.

De Bruijn, C., Veenman, J., Rutten, V., Teske, E., Van Nieuwstadt, R., & Van den Ingh, T. (2007). Clinical, histopathological and immunophenotypical findings in five horses with cutaneous malignant lymphoma. *Research in veterinary science, 83*(1), 63-72.

Desrochers, A., St-Jean, G., & Kennedy, G. A. (1994). Congenital cutaneous papillomatosis in a one-year-old Holstein. *The Canadian Veterinary Journal, 35*(10), 646.

Dietz, O., & Wiesner, E. (1982). *Diseases of the horse : a handbook for science and practice* Basel ; New York ; Sydney; Karger,: Fischer.

Diters, R., & Walsh, K. (1984). Feline basal cell tumors: a review of 124 cases. *Veterinary Pathology, 21*(1), 51-56.

Dorn, C. R., Taylor, D., & Schneider, R. (1971). Sunlight exposure and risk of developing cutaneous and oral squamous cell carcinomas in white cats. *Journal of the National Cancer Institute, 46*(5), 1073-1078.

Dzutsev, A., Goldszmid, R. S., Viaud, S., Zitvogel, L., & Trinchieri, G. (2015). The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. *European journal of immunology, 45*(1), 17-31.

Garrett, L. D. (2014). Canine mast cell tumors: diagnosis, treatment, and prognosis. *Veterinary Medicine: Research and Reports, 5*, 49-58.

Gnad, D., Sargeant, J. M., Chenoweth, P., & Walz, D. P. H. (2004). Prevalence of bovine leukemia virus in young, purebred beef bulls for sale in Kansas. *J Appl Res Vet Med, 2*, 215-219.

Godoy, G., Borges, V., Borges, J., Prata, L., Valadao, C., Marques, L., & Alessi, A. (2003). Metastasizing oral melanoma in a cow. *Encontro nacional de patologia veterinária, 39*(4), 276.

Goldschmidt, M. (1998). Melanocytic tumors. *World Health Organization International Histological Classification of Tumours of Domestic Animals*.

Goldschmidt, M., & Hendrick, M. (2002). Tumors of the skin and soft tissues. *Tumors in domestic animals*, 45-117.

Goldschmidt, M., & Hendrick, M. (2008). Tumors in Domestic Animals: Tumors of the Skin and Soft Tissues: Iowa State University Press, Ames Iowa.

Goldschmidt, M. H. (1998). Histological classification of epithelial and melanocytic tumors of the skin of domestic animals *WHO International*

Histological Classification of Tumors of Domestic Animals, 2nd series.

Hargis, A., Thomassen, R., & Phemister, R. (1977). Chronic dermatosis and cutaneous squamous cell carcinoma in the beagle dog. *Veterinary Pathology, 14*(3), 218-228.

Haspeslagh, M., Vlaminck, L. E., & Martens, A. M. (2016). Treatment of sarcoids in equids: 230 cases (2008–2013). *Journal of the American Veterinary Medical Association, 249*(3), 311-318.

Head, K., Else, R., & Dubielzig, R. (2002). Tumors of the alimentary tract. *Tumors in domestic animals*, 401-481.

Hewes, C. A., & Sullins, K. E. (2009). *Review of the treatment of equine cutaneous neoplasia*. Paper presented at the Proceedings of the 55th Annual Convention of the American Association of Equine Practitioners, Las Vegas, Nevada, USA.

Hosseini, E., Pedram, B., Bahrami, A. M., Moghaddam, M. H. J., Javanbakht, J., Ghomi, F. E., . . . Shafiee, R. (2014). Retracted Article: Cutaneous mast cell tumor (Mastocytoma): Cyto-histopathological and haematological investigations. *Diagnostic pathology, 9*(1), 9.

Jacobs, R., Messick, J., & Valli, V. (2002). Tumors of the hemolymphatic system. *Tumors in domestic animals, 4*, 119-198.

Kiupel, M., Webster, J., Bailey, K., Best, S., DeLay, J., Detrisac, C., . . . Goldschmidt, M. (2011). Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior. *Veterinary Pathology, 48*(1), 147-155.

Knottenbelt, D. (2003). *Basic principles of diagnosis and management of neoplasia in horses*. Paper presented at the Proceedings of the 9th International Congress SIVE.

Krick, E., Billings, A., Shofer, F., Watanabe, S., & Sorenmo, K. (2009). Cytological lymph node evaluation in dogs with mast cell tumours: association with grade and survival. *Veterinary and comparative oncology, 7*(2), 130-138.

Langenbach, A., McManus, P. M., Hendrick, M. J., Shofer, F. S., & Sorenmo, K. U. (2001). Sensitivity and specificity of methods of assessing the regional lymph nodes for evidence of metastasis in dogs and cats with solid tumors. *Journal of the American Veterinary Medical Association, 218*(9), 1424-1428.

Lunardi, M., de Alcântara, B. K., Otonel, R. A. A., Rodrigues, W. B., Alfieri, A. F., & Alfieri, A. A. (2013). Bovine papillomavirus type 13 DNA in equine sarcoids. *Journal of Clinical Microbiology, 51*(7), 2167-2171.

MacGillivray, K. C., Sweeney, R. W., & Piero, F. D. (2002). Metastatic melanoma in horses. *Journal of veterinary internal medicine, 16*(4), 452-456.

Marinković, D., Milčić-Matić, N., Jovanović, M., Vučićević, I., Nešić, S., Aničić, M., & Aleksić-Kovačević, S. (2015). Morphological Features and KIT Receptor Expression in Canine Cutaneous Mast Cell Tumor and Systemic Mastocytosis/Morfološke Karakteristike I Ekspresija KIT Receptora Kod Kutanih Mastocitoma I Sistemske Mastocitoze Pasa. *Acta Veterinaria, 65*(2), 226-237.

Marti, E., Lazary, S., Antczak, D., & Gerber, H. (1993). Report of the first international workshop on equine sarcoid. *Equine veterinary journal, 25*(5), 397-407.

Meuten, D. J. (2016). *Tumors in domestic animals*: John Wiley & Sons.

Meyer, J., Delay, J., & Bienzle, D. (2006). Clinical, laboratory, and histopathologic features of equine lymphoma. *Veterinary Pathology, 43*(6), 914-924.

Miller, M., Nelson, S., Turk, J., Pace, L., Brown, T., Shaw, D., . . . Gosser, H. (1991). Cutaneous neoplasia in 340

cats. *Veterinary Pathology*, *28*(5), 389-395.

Miller, M., Weaver, A., Stogsdill, P., Fischer, J., Kreeger, J., Nelson, S., & Turk, J. (1995). Cutaneous melanocytomas in 10 young cattle. *Veterinary Pathology*, *32*(5), 479-484.

Misdorp, W. (2002). Congenital tumours and tumour-like lesions in domestic animals. 1. Cattle A review. *Veterinary quarterly*, *24*(1), 1-11.

Misdorp, W. (2004). Mast cells and canine mast cell tumours. A review. *Veterinary quarterly*, *26*(4), 156-169.

Mittal, R., Rath, S., & Vemuganti, G. K. (2013). Ocular surface squamous neoplasia–Review of etio-pathogenesis and an update on clinico-pathological diagnosis. *Saudi Journal of Ophthalmology*, *27*(3), 177-186.

Müller, J.-M., Feige, K., Wunderlin, P., Hödl, A., Meli, M. L., Seltenhammer, M., . . . Heinzerling, L. M. (2011). Double-blind placebo-controlled study with interleukin-18 and interleukin-12-encoding plasmid DNA shows antitumor effect in metastatic melanoma in gray horses. *Journal of immunotherapy*, *34*(1), 58-64.

Nagy, D. W. (2006). *Decreasing perinatal bovine leukosis virus infection in calves*. University of Missouri--Columbia.

Naik, S., Balakrishnan, C., & Randelia, H. P. (1969). Epidemiology of horn cancer in Indian Zebu cattle: Breed incidence. *British Veterinary Journal*, *125*(5), 222-230.

Newman, S., Mrkonjich, L., Walker, K., & Rohrbach, B. (2007). Canine subcutaneous mast cell tumour: diagnosis and prognosis. *Journal of comparative pathology*, *136*(4), 231-239.

Ott, S., Johnson, R., & Wells, S. J. (2003). Association between bovine-leukosis virus seroprevalence and herd-level productivity on US dairy farms. *Preventive veterinary medicine*, *61*(4), 249-262.

Patnaik, A., Ehler, W., & MacEwen, E. (1984). Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs. *Veterinary Pathology*, *21*(5), 469-474.

Priester, W. A. (1980). *The occurrence of tumors in domestic animals*: US Department of Health and Human Services, Public Health Service, National ….

Proschowsky, H. F., Rugbjerg, H., & Ersbøll, A. K. (2003). Mortality of purebred and mixed-breed dogs in Denmark. *Preventive veterinary medicine*, *58*(1-2), 63-74.

Ramadan, R. (1975). Squamous cell carcinoma of the perineum of the goat. *British Veterinary Journal*, *131*(3), 347-350.

Ramos-Vara, J., Beissenherz, M., Miller, M., Johnson, G., Pace, L., Fard, A., & Kottler, S. (2000). Retrospective study of 338 canine oral melanomas with clinical, histologic, and immunohistochemical review of 129 cases. *Veterinary Pathology*, *37*(6), 597-608.

Scott, D., Miller, W., & Griffin, C. (2001). Neoplastic and non-neoplastic tumors. *Muller and Kirk's small animal dermatology*, 1289-1290.

Simonetti, O., Lucarini, G., Brancorsini, D., Nita, P., Bernardini, M. L., Biagini, G., & Offidani, A. (2002). Immunohistochemical expression of vascular endothelial growth factor, matrix metalloproteinase 2, and matrix metalloproteinase 9 in cutaneous melanocytic lesions. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *95*(9), 1963-1970.

Smedley, R., Spangler, W., Esplin, D., Kitchell, B., Bergman, P., Ho, H.-Y., . . . Kiupel, M. (2011). Prognostic markers for canine melanocytic neoplasms: a comparative review of the literature and goals for future investigation. *Veterinary Pathology*, *48*(1), 54-72.

Smith, S., Goldschmidt, M., & McManus, P. (2002). A comparative review of melanocytic neoplasms. *Veterinary Pathology, 39*(6), 651-678.

Spangler, W., & Kass, P. H. (2006). The histologic and epidemiologic bases for prognostic considerations in canine melanocytic neoplasia. *Veterinary Pathology, 43*(2), 136-149.

Sweet, M., Kirkham, N., Bendall, M., Currey, L., Bythell, J., & Heupel, M. (2012). Evidence of melanoma in wild marine fish populations. *PloS one, 7*(8).

Taintor, J., & Schleis, S. (2011). Equine lymphoma. *Equine Veterinary Education, 23*(4), 205-213.

Taylor, S., & Haldorson, G. (2013a). A review of equine mucocutaneous squamous cell carcinoma. *Equine Veterinary Education, 25*(7), 374-378.

Taylor, S., & Haldorson, G. (2013b). A review of equine sarcoid. *Equine Veterinary Education, 25*(4), 210-216.

Valentine, B. A. (2006). Survey of equine cutaneous neoplasia in the Pacific Northwest. *Journal of Veterinary Diagnostic Investigation, 18*(1), 123-126.

Villalobos, A. E. (2011). Assessment and treatment of nonpain conditions in life-limiting disease. *Veterinary Clinics: Small Animal Practice, 41*(3), 551-563.

Webster, J., Yuzbasiyan-Gurkan, V., Miller, R., Kaneene, J., & Kiupel, M. (2007). Cellular proliferation in canine cutaneous mast cell tumors: associations with c-KIT and its role in prognostication. *Veterinary Pathology, 44*(3), 298-308.

Welle, M. M., Bley, C. R., Howard, J., & Rüfenacht, S. (2008). Canine mast cell tumours: a review of the pathogenesis, clinical features, pathology and treatment. *Veterinary dermatology, 19*(6), 321-339.

Withrow, S. J., Page, R., & Vail, D. M. (2013). *Withrow and MacEwen's Small Animal Clinical Oncology-E-Book*: Elsevier Health Sciences.

Wobeser, B. K., Davies, J. L., Hill, J. E., Jackson, M. L., Kidney, B. A., Mayer, M. N., . . . Allen, A. L. (2010). Epidemiology of equine sarcoids in horses in western Canada. *The Canadian Veterinary Journal, 51*(10), 1103.