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REVIEW

Canine ocular neoplasia: a review

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Abstract

Ocular neoplasia is relatively rare in dogs but can have significant impact on vision, comfort, and longevity. Prognosis for life and for the globe varies with tumor type. In this review, the clinicopathologic features of the most common canine ocular neoplasms are detailed, with emphasis on histologic and immunohistochemical characteristics.

Key Words: canine, histopathology, immunohistochemistry, neoplasia, ocular, review

INTRODUCTION

Primary ocular neoplasms are uncommon in dogs relative to neoplasia affecting other organs.[1–4] Ocular neoplasms can cause loss or impairment of vision, discomfort, tissue destruction, and metastasis. Ocular neoplasia can be roughly divided into three categories: adnexal/ocular surface, intraocular, and orbital. The impact on the structure and function of the globe, therapeutic options, and prognosis varies with anatomic location of the neoplasm. As in other organs, neoplasms may be primary, arising from the tissue they affect, or secondary, arising from a distant tissue. Secondary neoplasia may be part of a metastatic or multicentric process. Primary ocular neoplasia is more common than secondary neoplasia.[1] Of the anatomic sites for ocular neoplasia, intraocular structures are most likely to be affected by secondary neoplasia.[1]

ADNEXAL/OCULAR SURFACE NEOPLASIA

Periocular skin

Periocular skin is affected by neoplasia similarly to skin elsewhere on the body. There are abundant resources available regarding the diagnosis and treatment of skin neoplasia, hence the discussion here will be deliberately brief.[5] Neoplasia with a predisposition for the head and neck areas is more likely to affect the periocular skin, including canine cutaneous histiocytoma, melanocytoma, sebaceous hyperplasia, adenoma and epithelioma, squamous and viral papillomas, trichoblastoma, and others.[5] These neoplasms are typically benign. The clinical and histopathologic features mimic those of similar neoplasms at other cutaneous sites. While some neoplasms may regress spontaneously, as in histiocytoma or viral papillomas, other may require therapeutic intervention.[6] The slowly progressive nature of some neoplasms, as in melanocytoma, makes benign neglect and careful monitoring a reasonable therapeutic option.[7] Surgical excision may be required in some cases where growth of the melanocytoma is noted but comes with the added challenge of maintaining eyelid structure and function.[7]

Eyelid margin

The meibomian glands of the eyelid margin are the adnexal structure most frequently affected by neoplasia, representing 44–70% of eyelid neoplasms.[4,6,8] Histologically, meibomian gland neoplasms can be categorized as adenomas, epitheliomas, and carcinomas, and all of which have a similar clinical appearance. Meibomian gland neoplasms appear clinically as tan, pink, gray, or black masses extending from the meibomian gland orifice. Occasionally, they will erupt through the palpebral conjunctiva. They may have a cobblestone or irregularly textured surface and will often hemorrhage when traumatized. If the tumor mass remains within the gland, it may obstruct the gland orifice, leading to glandular rupture and release of glandular lipid secretions into the surrounding tissue. A marked inflammatory response occurs and may cause the tumor to have a falsely large appearance.

Histologically, meibomian glands adenomas are similar to sebaceous adenomas of the skin (Fig. 1). They are well circumscribed and are often partially exophytic. They are comprised of variably sized lobules of meibomian cells that show normal maturation from small basal reserve cells at the periphery to mature large lipid-laden well-differentiated cells centrally. There are usually multifocal areas of

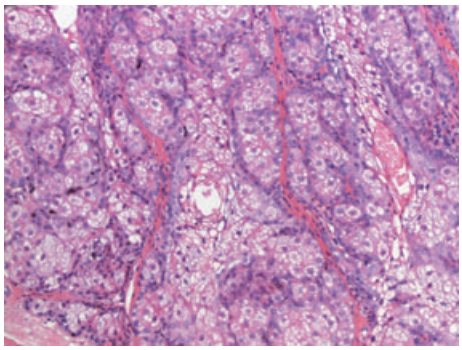

Figure 1. Meibomian gland adenoma. The mass is composed of well-differentiated lipid-laden cells with areas of cystic degeneration. HE. 200×.

cystic degeneration. Mitoses are limited to basal cells and are therefore rare to absent in neoplasms composed predominantly of mature cells. Melanization is variable and usually limited to basal cells. Meibomian adenomas usually include haphazardly arranged ducts that vary in number and size. The ducts are lined by squamous epithelium with scant keratinization. Meibomian gland adenomas can, but are infrequently, categorized as simple or compound/ductal, depending on the extent of ductular differentiation. The overlying epidermis is often hyperplastic and papillomatous and can mimic the appearance of a squamous papilloma. Commonly, rupture and leakage of lipid material elicits peritumoral lipogranulomatous inflammation. The inflammation consists of nodular infiltration of large numbers of macrophages and multinucleated giant cells that often contain acicular birefringent material with multifocal lipid lakes, visible as clear spaces.[2,4,5,8–12] The immunohistochemical profile of meibomian gland adenomas has not been established.

Meibomian epitheliomas have histologic features similar to cutaneous sebaceous epitheliomas (Fig. 2). They are well-circumscribed masses composed of densely packed sheets of small basal reserve cells with limited differentiation to lobules or single lipid-laden cells or ducts. The

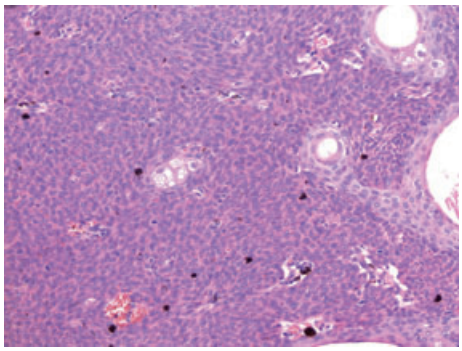

Figure 2. Meibomian gland epithelioma. The mass is composed predominately of basal cells with multifocal differentiation to lipid-laden cells and ducts. HE. 200×.

basal cells are small with scant eosinophilic cytoplasm and oval nuclei, stippled chromatin and often multiple nucleoli. The mitotic index is typically high, with >20 mitoses in 10 high-power fields (HPFs). Nuclear atypia and pleomorphism are minimal. The overlying epidermis is often hyperplastic, and lipogranulomatous inflammation may border and infiltrate masses with sufficient lipid content.[2,4,5,8–12]

Objective criteria to differentiate meibomian adenomas and epitheliomas have not been clearly established. Epitheliomas should have a 'preponderance' of basal cells, and some have suggested that 90% of the cells be of the basal type to warrant the diagnosis of epithelioma.[5,10] Although mitoses may be numerous, other features of malignancy are not observed with meibomian epitheliomas, and some authors include epitheliomas under the umbrella of benign meibomian adenomas. It is worth noting that some masses with features of meibomian epitheliomas have been published as carcinomas based on the number of mitoses.[4,11] True meibomian carcinomas do occur but are quite rare and show unequivocal features of malignancy (i.e. invasion and pleomorphism) in addition to numerous mitoses.[2,4,5,8–12] The immunohistochemical profile of meibomian gland epitheliomas has not been established.

The prognosis for life is excellent, and the prognosis for the globe is likewise excellent for meibomian gland adenomas, epitheliomas, and carcinomas with appropriate treatment. Treatment requires removal of the tumor, either by complete excision or by debulking and cryoablation.[13,14] Recurrence rates are similar among treatment methods.[14]

Conjunctiva

Melanocytic neoplasia Conjunctival melanocytic neoplasms appear clinically as pink to lightly pigmented to darkly pigmented masses of the palpebral, bulbar, and third eyelid conjunctiva. The histologic challenges of diagnosing of conjunctival melanocytic neoplasia as benign or malignant are similar to those at other sites. The mitotic index (MI) has been reported to be the best indicator of malignancy for conjunctival neoplasms, but a definitive cut-off has not been established. Identification of 3–4 mitoses in 10 HPFs has been suggested for mucosal melanocytic neoplasms at other sites and may be useful in the classification of conjunctival melanocytic neoplasia.[15,16]

Benign melanocytomas are well circumscribed and composed of heavily pigmented cells in which the nuclei are often obscured by the melanin. The growth patterns vary between and within neoplasms, and the cells may be polygonal or spindle. There is minimal anisokaryosis and anisocytosis within each cell type. The MI is usually very low, 0–1 in 10 HPFs. Junctional activity, nests of neoplastic cells within the overlying epithelium, is a common finding. Melanophages may be admixed with the neoplastic cells.[2,4,8,9,11,12] The immunohistochemical profile of

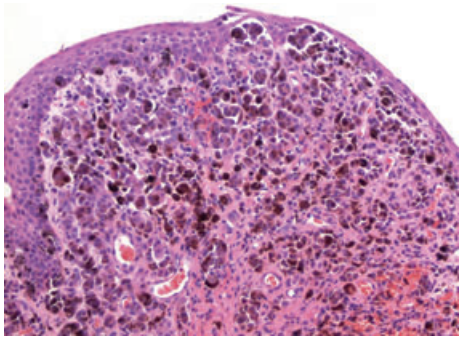

Figure 3. Conjunctival malignant melanoma. The neoplastic cells abut and invade the epithelium (junctional activity). The cells are large and polygonal with small amounts of melanin. HE. 200×.

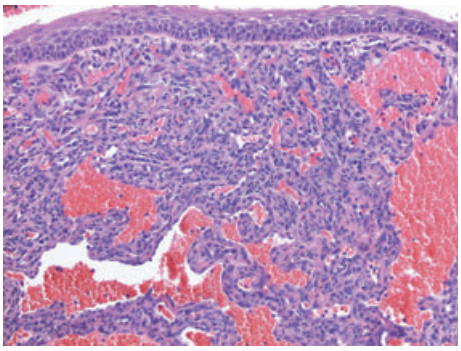

Figure 4. Conjunctival hemangiosarcoma. The mass consists of poorly formed vascular channels that vary in shape and size. HE. 200×.

conjunctival melanocytomas has not been established, but they can be expected to have an immunophenotype similar to melanocytomas at other locations and express vimentin, Melan-A, and PNL-2.[17–19]

Most conjunctival melanocytic neoplasms are malignant.[20] The masses are poorly circumscribed with stromal invasion and may be multifocal. The cells are polygonal to spindle cells and form various growth patterns (Fig. 3). Junctional activity is present in most masses where the overlying epithelium is intact. Pigmentation varies between and within neoplasms; malignant melanomas are mildly pigmented when compared to melanocytomas, and some may be amelanotic. There is moderate to severe anisokaryosis and anisocytosis. The MI is typically much higher than 4 in 10 HPFs. Foci of necrosis are common, and melanophages may infiltrate the neoplasms. The overlying epithelium is often ulcerated.[1,4,8,9,11,12] Conjunctival malignant melanomas are immunoreactive for Melan-A and S100, and there may be limited expression of kit (CD117).[2, 21] They can be expected to have an immunophenotype similar to malignant melanomas at other locations and express vimentin, Melan-A, and PNL-2.[17–19]

The prognosis for life and for the globe in conjunctival melanoma is guarded, as conjunctival lesions tend to be more malignant than periocular skin lesions. The confirmed metastasis rate has been reported as 17% and may be as high as 33.3%.[20] Local recurrence, even after aggressive surgical intervention, may occur. Wide surgical excision followed by cryotherapy, enucleation, and exenteration are treatment options.

Vascular neoplasia Vascular neoplasms appear clinically as smooth, raised, pink-to-red masses on the conjunctival surface. Vascular neoplasms are classified as hemangiomas or hemangiosarcomas. Hemangiomas are well-circumscribed masses composed of vascular channels lined by endothelial cells that are similar to those of normal vessels. The vascular channels lack the arrangement of smooth muscle and pericytes that form normal vessel walls. Mitoses are not observed. Most hemangiomas are of the cavernous type with large vascular channels; however, capillary hemangiomas do occur. Rarely, there may be irregular hyperplasia of the overlying epithelium (angiokeratoma).[9,11,12,22–29] Hemangiomas are routinely immunopositive for the endothelial cell marker Factor VIII and are immunoreactive for CD31.[2,11,16,30,31] Hemangiomas are also immunoreactive for p16, PCNA, and estrogen receptor alpha. Most hemangiomas are immunoreactive for pAkt, and some are immunoreactive for p21, Cyclin D, and telomerase. Hemangiomas are negative for p53.[32]

Hemangiosarcomas are variably infiltrative masses composed of anastomosing irregularly shaped and sized vascular channels (Fig. 4). The vascular channels are lined by plump endothelial cells that often bulge in the lumen and lack the arrangement of smooth muscle and pericytes that comprise a normal vessel. Pleomorphism is variable, but the neoplastic cells do not have features of normal endothelium. The mitotic index depends in part on cell density within the examined fields, but is usually low. Most conjunctival hemangiosarcomas are well differentiated, and distinction from hemangiomas is not always straightforward.[9,11,12,23,24,28,33,34] Hemangiosarcomas, like hemangiomas, are immunopositive for the endothelial cell markers Factor VIII and CD31.[2,11,33] In addition, hemangiosarcomas are immunoreactive for p16, PCNA, and estrogen receptor alpha, most for pAkt, and some are immunoreactive for p21 and telomerase. Hemangiosarcomas are negative for p53 and Cyclin D.[32]

The prognosis for life and for the globe in hemangioma is good, with complete surgical excision being curative in most cases.[28] The prognosis for life in hemangiosarcoma is also good; however, there is an increased risk of local recurrence after surgical excision.[28] Wide surgical excision with adjunctive cryotherapy has been recommended.[28]

Mast cell tumors Conjunctival mast cell tumors present clinically as smooth, firm, and subconjunctival masses.[35] Local conjunctival hyperemia or conjunctival hemorrhages may be present, and the tumor may fluctuate in size. Conjunctival mast cell tumors are histologically similar to

those in the skin. The masses are typically well circumscribed and composed of sheets of round cells. The cells have distinct borders and often contain cytoplasmic granules. Eosinophils may be admixed with the neoplastic cells. Edema is a common finding.[9,29,35–38] The cytologic features of conjunctival mast cells are most often similar to those of Grade I-II (Patnaik system) [39] or low grade (2-tier system) [40] skin neoplasms. However, some features of the grading systems are difficult to apply to the conjunctiva, and the significance of grading systems developed for cutaneous mast cell tumors has not been determined for conjunctival neoplasms. Similarly, prognostic markers (kit(CD117), kit mutations, ki-67) used in cutaneous mast cell tumors have not been investigated in conjunctival mast cell tumors.

The prognosis for life and for the globe with mast cell tumor is good. While local recurrence is occasionally observed after complete and incomplete excision, metastasis appears rare.[35] Surgical excision is reported to be curative, and adjunctive therapy may or may not be decrease recurrence.[35]

Third eyelid gland adenoma/adenocarcinoma Third eyelid gland adenomas and adenocarcinoma appear similar clinically. Protrusion of the third eyelid is noted, with a pink, firm mass expanding the body of the third eyelid.[41] The space-occupying effect of the mass may be associated with exophthalmos, strabismus, or enophthalmos. Most neoplasms of the gland of the third eyelid are histologically malignant. Third eyelid gland adenocarcinomas are expansile and variably infiltrative masses. Some are well differentiated and composed of tubules that resemble normal gland tissue, and others are mostly solid with only rare tubules (Fig. 5). Squamous metaplasia is a common finding. Rare neoplasms include myoepithelial and/or stromal elements. The neoplastic cells are cuboidal to columnar in well-differentiated tubular neoplasms and some solid masses. Small 'basal' cells with scant cytoplasm may be a significant component of some solid masses. Pleomorphism is mild even in solid neoplasms. The mitotic index is highly variable. Some masses may be associated with lymphocytic inflammation. Most texts only describe the malignant form, but rare third eyelid gland adenomas have been noted.[2,4,9,11,12,41] Third eyelid gland adenocarcinomas are cytokeratin positive.[2]

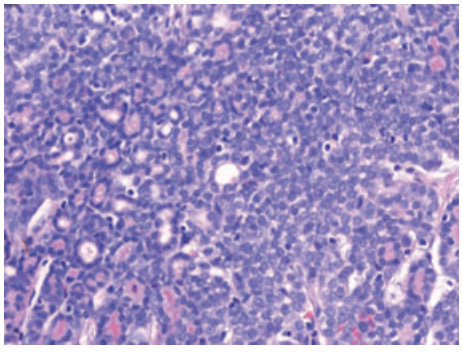

Figure 5. Third eyelid gland adenocarcinoma. The mass is mostly solid with multifocal tubules. HE. 400×.

The prognosis for life with third eyelid gland adenomas and adenocarcinomas is good with complete surgical excision. Metastasis and death in one case with a highly invasive incompletely excised adenocarcinoma has been reported; however, complete excision can be expected to be curative.[41] If removal of the third eyelid alone is sufficient to obtain clean margins, the prognosis for the globe is good; however, exenteration may be required for complete excision.[41]

Cornea/sclera

Epibulbar/limbal melanocytic neoplasms Epibulbar or limbal melanocytic neoplasms appear clinically as darkly pigmented masses arising from the limbus and expanding into the adjacent cornea and sclera or as masses arising posterior to the limbus and expanding into the adjacent sclera.[42] Limbal melanocytic neoplasms are presumed to arise from the melanocytes that demarcate the limbus at the junction of the corneal stroma and sclera. They expand along the planes of least resistance toward the conjunctiva readily and into the adjacent corneal stroma minimally. Histologically, almost all are benign melanocytomas. These broad-based, nodular neoplasms are composed of discohesive heavily pigmented plump polyhedral cells often admixed with fewer pigmented spindle cells. There is no atypia, and mitoses are rare to absent. Necrosis occurs in approximately 20% of cases. These masses grow by expansion and may extend intraocularly. Rare histologically malignant limbal melanomas have been described, and some otherwise benign neoplasms may include areas with cells that are less pigmented or amelanotic and mitotically active.[1,4,8,9,11,12,42–48] The immunohistochemical profile of limbal melanocytomas has not been established, but they can be expected to have an immunophenotype similar to melanocytomas at other locations, expressing vimentin, Melan-A, and PNL-2.[17–19]

The prognosis for life with limbal melanocytic neoplasia is excellent. Limbal melanocytomas have bimodal age distribution, and tumors in older dogs may be particularly slow to progress.[42] Benign neglect and careful monitoring may be warranted in such cases. Surgical excision can preserve the globe in cases with more rapid progression.[46,49–52] Photocoagulation may also be effective in arresting tumor progression.[53]

Corneal squamous cell carcinoma Squamous cell carcinoma (SCC) of the cornea can have a varied clinical appearance. It may present as a discrete, pink, cobblestone textured mass, or a more diffuse pink mass associated with significant corneal vascularization.[54] SCC is more likely to

occur in corneas with chronic keratitis, and some association with the administration of topical immunomodulators has been proposed.[54–57] Corneal squamous cell carcinomas have histologic features similar to those in other locations. In the cornea, masses are usually exophytic and variably infiltrative. Approximately 30% of described cases represent the *in situ* form of squamous cell carcinoma. The neoplasms consist of nests and trabeculae with multifocal dyskeratosis and keratin pearl formation. The neoplastic cells are large, have distinct cell borders and abundant cytoplasm. Mitoses are numerous while pleomorphism is variable. When present, extension in the stroma is superficial. The adjacent corneal epithelium may be hyperplastic/dysplastic and is often pigmented. Corneal stromal inflammation and neovascularization are common findings when the stroma is available for histopathologic evaluation.[9,11,54–56,58–62] In the few corneal squamous cell carcinomas assessed, immunoreactivity for cytokeratin (1/1), e-cadherin (1/1), and GADD45 (1/1) with rare immunopositive cells for caspase 3 was detected. One of three masses was positive for p53.[56,61]

The prognosis for life with corneal squamous cell carcinoma appears to be good. The prognosis for the globe is dependent on early detection and surgical intervention. Surgical excision by keratectomy is recommended, and adjunctive therapy may be useful in decreasing recurrence.[54–58]

Other ocular surface neoplasia

Other neoplasms or masses that may affect the conjunctiva and ocular surface include benign dermoids, squamous and viral papillomas, cysts, and inflammatory masses such as nodular granulomatous episcleritis, onchocerciasis, foreign body reactions, and others. Malignant neoplasms include conjunctival squamous cell carcinoma, which is rare in dogs compared with other species, lymphoma, and transmissible venereal tumor.[2,4,9,12,57,63–66] Clinical appearance and prognosis vary with tumor type.

INTRAOCULAR NEOPLASIA

Uvea

Uveal melanocytic neoplasia It is difficult to differentiate benign from malignant uveal melanocytic neoplasia based on clinical appearance. Clinically, this tumor type has a variable appearance.[47,67] Anterior uveal melanocytic neoplasms may appear as a mass expanding the iris and extending into the anterior chamber or as a mass posterior to the iris that anteriorly displaces the iris face. Occasionally, the first clinical sign of an anterior uveal melanocytic neoplasm is thinning of the sclera with a pigmented mass visible expanding into the sclera. Uveitis is usually not a feature of anterior uveal melanocytic neoplasia; however, secondary glaucoma may be present.[48,68–74] Masses are typically heavily pigmented, but may be nonpigmented. Choroidal melanocytic neoplasms appear as focal pigmented subretinal masses that may be associated with retinal detachment.

Table 1. Relative frequency of intraocular and optic nerve neoplasia in dogs in two veterinary pathology databases

Neoplasm	Database A*	Database B*	Total	%
Uveal melanocytoma (total)	1090	356	1446	41.5
Anterior uvea	1025	336	1361	
Choroidal	65	20	85	
Iridociliary adenoma	592	142	734	21.1
Uveal malignant melanoma (total)	334	124	458	13.1
Anterior uvea	323	120	443	
Choroidal	11	4	15	
Lymphoma	188	30	218	6.3
Metastatic neoplasia†	169	35	204	5.9
Iridociliary adenocarcinoma	116	36	152	4.4
Optic nerve meningioma	60	37	97	2.8
Histiocytic sarcoma	54	36	90	2.6
Schwannoma of blue-eyed dogs/peripheral nerve sheath tumor	43	6	49	1.4
Astrocytoma	21	3	24	0.7
Medulloepithelioma	24	0	24	0.7
Total	2691	805	3496	

*Database A[9]; Database B from author PL (Jan 2006-Sept 2012).
†Excluding lymphoma and histiocytic sarcoma.

Benign uveal melanocytomas are most common in the iris and ciliary body, typically affecting both. A review of two large ocular pathology databases shows that only 6% of uveal melanocytomas principally affect the choroid (Table 1). Melanocytomas of the anterior uvea readily efface the iridocorneal angle. Many expand along the corneoscleral meshwork which extends anterior to the termination of Descemet's membrane and blend with the deep peripheral corneal stroma. Scleral and extrascleral extension is common for both anterior uveal and choroidal melanocytomas and is not a feature that is indicative of malignancy.

All melanocytomas have a similar histologic appearance independent of their origin in the iris, ciliary body, or choroid. The neoplasms are composed of variable proportions of heavily pigmented spindle cells and discohesive heavily pigmented plump polyhedral cells (Fig. 6). The spindle cell population has indistinct cell borders, small to moderate amounts of pigmented cytoplasm, and oval nuclei often with one nucleolus. There is minimal anisokaryosis and anisocytosis. Mitoses are rare to absent (<4 in 10 HPF). The plump polyhedral cells are large with distinct cell borders, abundant pigmented cytoplasm, and central to peripheralized round nuclei. There is severe anisocytosis but minimal anisokaryosis. Mitoses are not present in the plump polyhedral cells. These plump polyhedral cells are melanocytes, not melanophages, and contain melanomas/premelanoses. Free individualized pigmented cells may be seen in the anterior and posterior

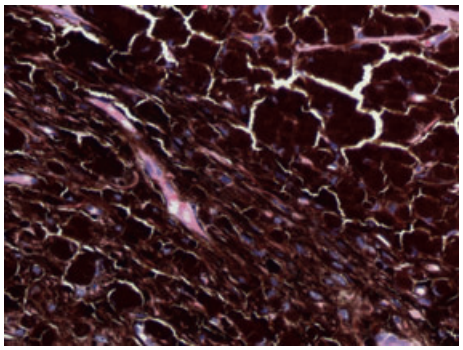

Figure 6. Uveal melanocytoma. The mass is composed of heavily pigmented plump polyhedral cells and heavily pigmented spindle cells. HE. 400×.

chambers and vitreous. Necrosis and infiltration of melanophages are common. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings. Retinal detachment is expected with choroidal melanocytomas.[72–76] The immunohistochemical profile of uveal melanocytomas has not been clearly established, but they can be expected to have an immunophenotype similar to melanocytomas at other locations and express vimentin, Melan-A, PNL-2, etc.[17–19] Uveal melanocytoma may express Cox-2 and monocarboxylate transporter 1.[77,78]

Uveal malignant melanoma is more common in the anterior uvea than in the choroid. Only 3% of uveal malignant melanomas are choroidal in origin. Approximately 25% of anterior uveal melanocytic neoplasms and 15% of choroidal melanocytic neoplasms are malignant (Table 1). The mitotic index is the most reliable parameter in the diagnosis of malignant melanoma. A threshold of four mitoses in 10 HPF is most widely used to establish malignancy in uveal melanocytic neoplasms. As with uveal melanocytomas, expansion along the corneoscleral meshwork in the sclera and in extrascleral tissues is common. Uveal malignant melanomas are composed of spindle cells to polygonal cells (Fig. 7). There is moderate to severe anisokaryosis and anisocytosis. Plump polyhedral cells may be present in low numbers. The spindle and polygonal cells are often only subtly pigmented. Malignant melanomas are less pigmented than their benign counterpart and can be amelanotic. Necrosis and infiltration of melanophages are common. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings. Anterior uveal malignant melanomas that extend in the choroid and choroidal malignant melanoma may cause retinal detachment. There are currently no histologic features that can reliably predict metastasis.[44,45,47,48,67,69,71,75,79–85] In the few reports with immunohistochemistry, uveal malignant melanoma is Melan-A immunoreactive with some expression of Cox-1 and Cox-2.[77,80,86] Uveal neoplasms are expected to share the immunophenotype of malignant melanomas at other locations.[17–19]

The prognosis for life with uveal melanocytoma is considered good, although the prognosis for the globe is poor as enucleation is frequently required, particularly in those eyes that develop secondary glaucoma.[44,45,47,48] Photocoagulation has been reported, with variable success in arresting tumor progression.[87,88] The prognosis for life with uveal malignant melanoma is guarded, and the prognosis for the globe is poor, as enucleation is frequently required, particularly in those eyes that develop secondary glaucoma.[44,45,48,67,79,80,83–85,89,90] The prognosis for a choroidal melanocytic neoplasm is based on its malignancy; most are benign choroidal melanocytomas tend to behave in a benign manner, whereas the more rare malignant tumors have a poorer prognosis.[68–74,76]

Ocular melanosis (diffuse uveal melanosis and pigmentary glaucoma) is a unique condition that must be distinguished from uveal melanocytomas and malignant melanomas. Clinically, ocular melanosis appears as diffuse pigmentation of the uveal tract.[91] In its early stages, the pigmentation may be discrete and multifocal but inevitably progresses to coalescing, diffuse pigmentation. Pigment may be visible in the fundus and through the sclera. It is unclear if ocular melanosis is truly neoplastic.[92] It is characterized by diffuse uveal infiltration of large plump, pigment-laden cells predominantly within the anterior uvea

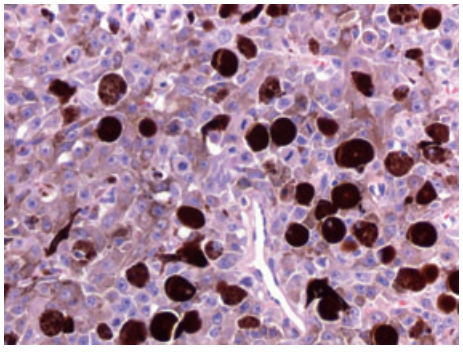

Figure 7. Uveal malignant melanoma. The polygonal cells are slightly pigmented and show pleomorphism. Numerous mitoses are present. HE. 400×.

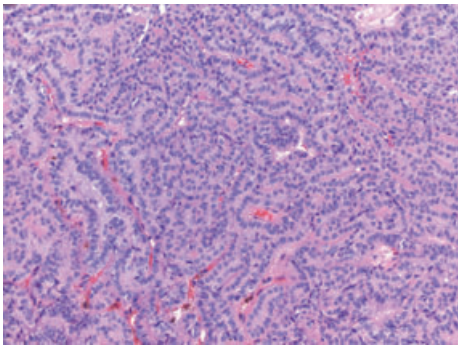

Figure 8. Iridociliary adenoma. The neoplastic cells form cords and nests. HE. 200×.

and anterior sclera without formation of a distinct mass (Fig. 8). Both melanocytes and melanophages contribute to the uveal expansion.[4,9,12,92,93] The melanocytes have a unique immunophenotype that differs from normal melanocytes with positive immunoreaction for vimentin and variable HMB-45 and microphthalmia transcription factor (MITF) immunoreactivity, but negative staining with Melan-A and S100. The melanophages are CD18 positive.[92,93]

Iridociliary neoplasia Clinically, neoplasia of the ciliary body epithelium appears as nonpigmented to lightly pigmented pink masses that may protrude into the pupillary aperture and displace the iris face anteriorly.[94] Dyscoria, lens subluxation, cataract, and retinal detachment may be observed, and secondary glaucoma may be present. Benign tumors cannot be clinically differentiated from malignant tumors. Benign ciliary body adenomas typically arise from the ciliary body epithelium and may involve the iris. Most expand in the posterior chamber, and some will extend in the ciliary body and iris. The masses are predominately nonpigmented, but pigment can be found in some neoplastic cells of most neoplasms. A small subset of benign iridociliary tumors is heavily pigmented. The neoplasms are composed predominately of cords and nests with tubules, solid sheets, and occasionally cysts (Fig. 9). Tubules and cysts may contain hyaluronic acid. The cuboidal cell population has distinct cell borders, moderate amounts of cytoplasm, and oval nuclei. There is usually mild anisokaryosis and anisocytosis although scattered cells may exhibit some atypia. Mitoses are uncommon (usually less than 5 in 10 HPF). Neoplastic cell produces PAS-positive basement membrane material. Intraocular hemorrhage, pre-iridal fibrovascular membranes, asteroid hyalosis, and glaucoma are frequent secondary findings.[1,2,4,8,9,11,12,29,94–96]

Mimicking normal neuroepithelium, iridociliary adenomas are immunoreactive for vimentin and neuron-specific enolase (NSE) with variable immunopositivity for S100, glial fibrillary acidic protein (GFAP), and desmin. There is also immunoreaction to telomerase reverse transcriptase (TERT), and some neoplasms express cytokeratins.[2,4,9,97,98]

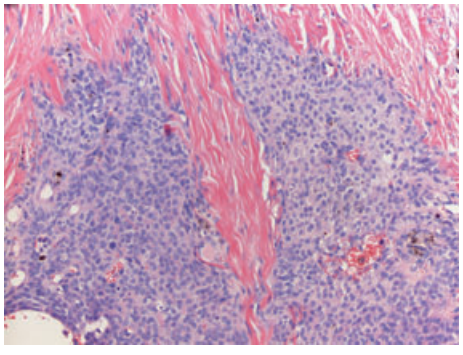

Figure 9. Iridociliary adenocarcinoma. The mostly solid mass extends in the sclera. HE. 200×.

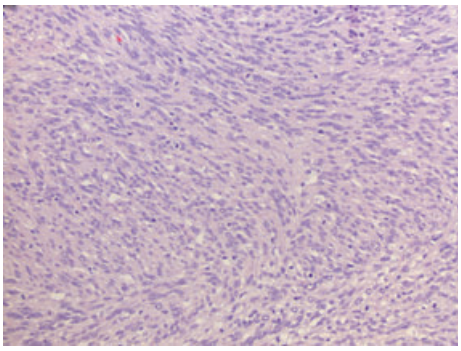

Figure 10. Uveal schwannoma of blue-eyed dogs. The spindle cells form interlacing bundles and streams. Numerous mitoses are present. HE. 200×.

Malignant iridociliary neoplasms (ciliary body adenocarcinomas) are similar to their benign counterpart. They typically arise from the ciliary body epithelium and will extend in the ciliary body and iris, and malignant iridociliary neoplasms will invade the sclera (Fig. 10). Invasion of the sclera is a major criteria of malignancy for malignant iridociliary neoplasms. Approximately 15% of iridociliary neoplasms can be classified as malignant (Table 1). The masses are predominately nonpigmented, but pigment can be found in some malignant iridociliary tumors. The neoplasms are composed predominately of nests and cords often with solid sheets. Tubules and cysts are less common than in benign tumors. The cuboidal cell population has distinct cell borders, moderate amounts of cytoplasm, and oval nuclei. There is moderate to severe anisokaryosis and anisocytosis. The mitotic index is highly variable and can be low but is typically increased compared with benign tumors (more than 5 in 10 HPF). Production of PAS-positive basement membrane material is usually present in at least portions of the mass. There is currently no histologic feature that can reliably predict metastasis. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings.[1,2,4,8,9,11,12,29,70,94,99,100]

Iridociliary adenocarcinomas are immunoreactive for vimentin, NSE and TERT with variable immunopositivity for S100, cytokeratin, GFAP and desmin. Malignant iridociliary neoplasms have increased TERT expression and are more likely to express cytokeratin than benign tumors.[2,4,9,97]

The prognosis for life with ciliary body adenomas and adenocarcinomas is good, although the prognosis for the globe is poor as enucleation is required in most cases.[95] Surgical excision, chemotherapy and photocoagulation have been reported as therapeutic options.[88,101]

Medulloepitheliomas are less common than ciliary body adenomas/adenocarcinomas. Clinically, medulloepitheliomas have a similar presentation to ciliary body adenomas

and adenocarcinomas.[102] Retinal detachment may be present depending on the location from which the tumor arises. Medulloepitheliomas are rare neoplasms of the canine globe that typically arise from the ciliary body. The neoplastic cells form loose sheets and poorly organized multilayered rosette-like structures with a central cavity. True Flexner–Wintersteiner and Homer–Wright rosettes may be present. The neoplasms are composed of small hyperchromatic stellate to round cells similar to those found in other primitive neuroectodermal tumors. Some areas may have features resembling ciliary processes or retina. Medulloepitheliomas may be termed teratoid when the neoplasm contains heterotopic elements that are not normal derivative of the ocular embryonic development.[1,2,4,8,9,11,12,29,94,102–105] Medulloepitheliomas are immunoreactive for TERT with limited immunopositivity for cytokeratin, vimentin and CD99. One case was negative for S100, NSE, triple neurofilament (TNF), GFAP, synaptophysin and ki-67.[97,102]

The prognosis for life is generally good, although metastasis is reported, and the prognosis for the globe is poor as enucleation is required in most cases.[4,102–105]

Schwannomas of blue-eyed dogs (peripheral nerve sheath tumors, 'spindle cell tumors of blue-eyed dogs') The clinical appearance of schwannomas of blue-eyed dogs/peripheral nerve sheath tumors is infrequently described in the peer-reviewed literature.[106–108] Moreover, some of these neoplasms may not be recognized clinically and are diagnosed when histopathology of the enucleated globe is performed.[106,107] Histologically, they typically arise in the iris and extend in the ciliary body. The morphologic, immunohistochemical and electron microscopy findings are all consistent with a schwannoma. The masses are nonpigmented and composed of interlacing bundles, streams and whorls. Antoni A and B patterns are usually recognized. The spindle cells have indistinct cell borders, scant amounts of cytoplasm and oval nuclei. Pleomorphism and mitotic index are variable. Approximately half of the neoplasms are well differentiated with a low mitotic index. Other masses may show marked atypia with numerous mitoses. Intraocular hemorrhage, pre-iridal fibrovascular membranes, and glaucoma are frequent secondary findings.[2,9,12,106–109] Schwannomas of blue-eyed dogs/peripheral nerve sheath tumors are immunoreactive for vimentin and S100. Most are immunopositive for GFAP and PGP 9.5. There is variable expression of laminin, GADD5, p53, PCNA, anti-UVssDNA, and TERT. The neoplastic cells are immunonegative for MITF, CD34, skeletal muscle actin and TNF, and usually immunonegative for Melan-A, smooth muscle actin and desmin.[9,106–109] The prognosis for life for this tumor type is not well understood with only one published case of metastasis, however the prognosis for the globe is considered poor as enucleation is required in most patients.[106,108]

Metastatic neoplasia The clinical appearance of metastatic neoplasia is variable, and may include anterior uveitis, discrete masses of the uveal tract or secondary glaucoma. Lymphoma and histiocytic sarcoma are the most common metastatic neoplasms to the canine globe (Table 1). Mammary adenocarcinomas are the most common secondary epithelial neoplasms. Hemangiosarcoma, malignant melanoma and osteosarcoma are common nonleukocytic sarcomas that spread to the eye. Metastases most often involve the iris and ciliary body in dogs. There are two general patterns of metastasis to the canine globe: diffuse expansion and effacement of the uveal tract and mass formation or multifocal expansion of the uveal tract often with carpeting of the iris and ciliary body. Lymphoma and histiocytic sarcoma will typically expand and efface the anterior uveal tract. Lymphoma will also readily extend in the choroid and retina or other structures. Carcinomas and nonleukocytic sarcomas more often will form multifocal masses and occlude blood vessels. Many will carpet or line the iris and ciliary body occasionally extending to cover the posterior cornea or retina (Fig. 11). Immunohistochemistry may be helpful to determine the histogenesis of poorly differentiated metastases.[1,2,4,8,9,11,12,90,110–113] The prognosis for life varies with the tumor type. The prognosis for the globe is considered poor as enucleation may be required, blinding sequelae such as retinal detachment

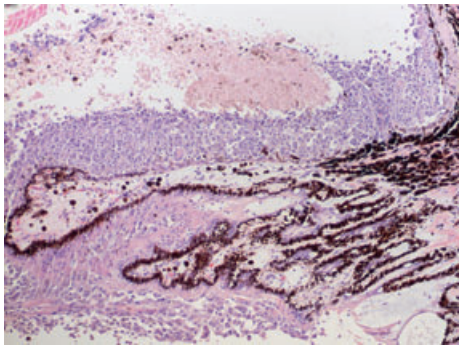

Figure 11. Metastatic oral malignant melanoma. The pleomorphic neoplastic cells line the ciliary processes. HE. 100×.

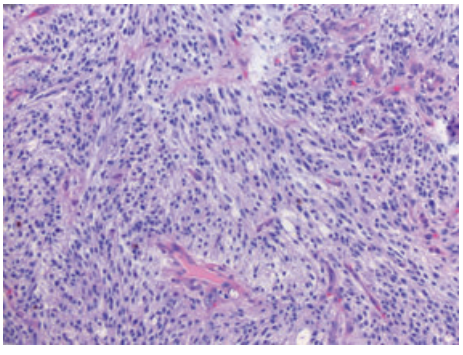

Figure 12. Retinal astrocytoma. The spindle cells have fibrillar cytoplasm and form bundles and fascicles. HE. 200×.

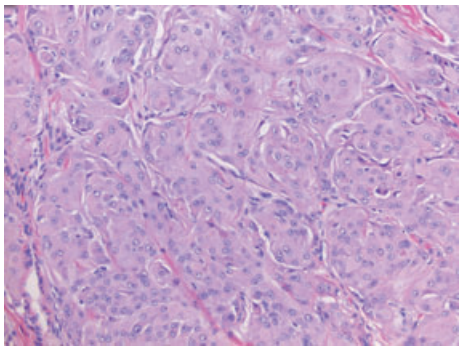

Figure 13. Orbital meningioma. The large polygonal cells have abundant cytoplasm and form nests. HE. 200×.

may develop or painful sequelae such as glaucoma may occur.

Retina/optic nerve

Astrocytomas (gliomas) Clinically, astrocytomas appear as a discrete mass in the fundus or more frequently, retinal detachment with secondary vitreal hemorrhage, hyphema, and glaucoma.[114] Astrocytomas may arise in the retina or optic nerve and often involve both. Approximately 40% will invade the choroid. The masses are nonpigmented and composed of interlacing bundles and fascicles with a delicate fibrovascular stroma (Fig. 12). The spindle cells have indistinct cell borders, moderate amounts of fibrillar eosinophilic cytoplasm, oval nuclei and often multiple nucleoli. Pleomorphism and mitotic index are variable but most masses are high grade astrocytomas with severe anisokaryosis and anisocytosis and high mitotic index. Retinal detachment, intraocular hemorrhage, pre-iridal fibrovascular membrane and glaucoma are frequent secondary findings.[9,114–117] Astrocytomas are immunoreactive for vimentin, most are immunopositive for GFAP, and there may be expression of NSE and S100. The neoplastic cells are immunonegative for Melan-A and TNF.[9,114–116] The prognosis for life is considered good with rare regional invasion reported, although the prognosis for the globe is poor as enucleation is required in most patients.[114,117]

ORBITAL NEOPLASIA

Orbital meningiomas (optic nerve meningiomas)
Clinically, orbital meningiomas are associated with exophthalmos and vision loss.[118] Papilledema or swelling of the optic nerve head may also be observed. Orbital meningiomas likely arise from extradural nests of arachnoid cells. The neoplasms typically extend and expand the orbital connective tissue. The masses may compress but do not invade the optic nerve. Rarely, there may be extension in the sclera or choroid, or through the optic foramen into the calvarium. The neoplastic cells form sheets and nests with subtle whorls. The cells are large and polygonal with distinct cell borders, large amounts of eosinophilic 'glassy' cytoplasm, and oval nuclei (Fig. 13). There is mild anisokaryosis and anisocytosis. The mitotic index is low (often 0 or 1 in 10 HPF). In most masses, there are foci of myxomatous, chrondroid, and/or osseous metaplasia. Optic nerve atrophy and degeneration and retrograde retinal atrophy with loss of ganglion cells are frequent secondary findings. Larger masses may cause bone remodeling.[2,9,29,118–121] Orbital meningiomas are immunoreactive for vimentin and NSE. Some are immunopositive for S100, e-cadherin, and GFAP. The neoplastic cells are immunonegative for cytokeratin.[2,9,118,120–122] The prognosis for life is fair to guarded, as local recurrence may occur. The prognosis for the globe is poor, as enucleation is required in many cases.[118]

Lobular orbital adenomas
Clinically, lobular orbital adenomas present as exophthalmos, third eyelid protrusion, subconjunctival mass effect, and periocular swelling.[123] Lobular orbital adenomas arise from the lacrimal or salivary glands. The neoplasms are multilobular and composed of nests and acini with scant stroma. The lobules lack ducts, and this feature is essential to making the diagnosis of lobular orbital adenoma. The cuboidal cell population has distinct cell borders, moderate amounts of cytoplasm that is often granular, and oval nuclei. There is minimal anisokaryosis and anisocytosis, and the cells essentially have features of normal tissue. Mitoses are absent.[9,11,123] The immunohistochemical profile of lobular orbital adenomas has not been established. The prognosis for life with lobular orbital adenoma appears guarded, as local recurrence is common.[123] The prognosis for the globe is guarded to poor, as exenteration is recommended to decrease recurrence.

Other orbital neoplasia
Any of the tissue components of the orbit may give rise to neoplasms such as osteosarcoma, multilobular tumor of bone, fibrosarcoma, liposarcoma, rhabdomyosarcoma, salivary-lacrimal adenocarcinoma, metastatic disease, and others. The features of these neoplasms are similar to those at other sites.[4,9,11,12,124–126]

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REFERENCES

1. Dubielzig RR. Ocular neoplasia in small animals. *The Veterinary Clinics of North America Small Animal Practice* 1990; **20**: 837–848.
2. Dubielzig RR. Tumors of the eye. In: *Tumors in Domestic Animals*, 4th ed. (ed. Meuten DJ). Iowa State Press: Ames, IA; 2002.
3. Miller PE, Dubielzig RR. Ocular tumors. In: *Small Animal Clinical Oncology*, 5th ed. (eds. Withrow SJ, Vail DM, Page RL). Elsevier-Saunders: St. Louis, 2013; 597–607.

4. Wilcock BP. Eye and ear. In: *Pathology of Domestic Animals*. (ed. Maxie MG). Elsevier-Saunders: Philadelphia, PA, 2007; 459–552.
5. Gross TL, Ihrke PJ, Walder EJ *et al. Skin Diseases of the Dog and Cat*, 2nd edn.. Blackwell Science, Ames, IA, 2005.
6. Roberts SM, Severin GA, Lavach JD. Prevalence and treatment of palpebral neoplasms in the dog: 200 cases (1975–1983). *Journal of the American Veterinary Medical Association* 1986; **189**: 1355–1359.
7. Aquino SM. Management of eyelid neoplasms in the dog and cat. *Clinical Techniques in Small Animal Practice* 2007; **22**: 46–54.
8. Peiffer RLJ. Adnexal and ocular neoplasms. In: *Pathobiology of the Aging Dog*. (eds. Mohr U, Carlton WW, Dungworth DL, Benjamin SA, Capen CC, Hahn FF). Iowa State University Press: Ames, IA, 2001.
9. Dubielzig RR, Ketring KL, McLellan GJ *et al. Veterinary Ocular Pathology*. Elsevier-Saunders, Philadelphia, PA, 2010.
10. Goldschmidt MH, Dunstan RW, Stannard AA *et al. Histological Classification of Epithelial and Melanocytic Tumors of the Skin in Domestic Animals*. Armes Forces Institute of Pathology, Washington, DC, 2002.
11. Peiffer RLJ, Simons KB. *Ocular Tumors in Animals and Humans*. Iowa State Press, Ames, IA, 2002.
12. Wilcock B, Dubielzig RR. *Histological Classification of Ocular and Otic Tumors of Domestic Animals*. Armed Forces Institute of Pathology, Washington, DC, 2002.
13. Stades FC, Gelatt KN. Diseases and Surgery of the Canine Eyelid. In: *Veterinary Ophthalmology*, 4th ed. (ed. Gelatt KN). Blackwell Publishing: Ames, IA, 2007; 1672.
14. Holmberg DL. Cryosurgical treatment of canine eyelid tumors. *The Veterinary Clinics of North America Small Animal Practice* 1980; **10**: 831–836.
15. Esplin DG. Survival of dogs following surgical excision of histologically well-differentiated melanocytic neoplasms of the mucous membranes of the lips and oral cavity. *Veterinary Pathology* 2008; **45**: 889–896.
16. Smedley RC, Spangler WL, Esplin DG *et al.* Prognostic markers for canine melanocytic neoplasms: a comparative review of the literature and goals for future investigation. *Veterinary Pathology* 2011; **48**: 54–72.
17. Ramos-Vara JA, Miller MA. Immunohistochemical identification of canine melanocytic neoplasms with antibodies to melanocytic antigen PNL2 and tyrosinase: comparison with Melan A. *Veterinary Pathology* 2011; **48**: 443–450.
18. Smedley RC, Lamoureux J, Sledge DG *et al.* Immunohistochemical diagnosis of canine oral amelanotic melanocytic neoplasms. *Veterinary Pathology* 2011; **48**: 32–40.
19. Smith SH, Goldschmidt MH, McManus PM. A comparative review of melanocytic neoplasms. *Veterinary Pathology* 2002; **39**: 651–678.
20. Collins BK, Collier LL, Miller MA *et al.* Biologic behavior and histologic characteristics of canine conjunctival melanoma. *Progress Veterinary Comparative Ophthalmology* 1993; **3**: 135–140.
21. Newman SJ, Jankovsky JM, Rohrbach BW *et al.* C-kit expression in canine mucosal melanomas. *Veterinary Pathology* 2012; **49**: 760–765.
22. Buyukmihci N, Stannard AA. Canine conjunctival angiokeratomas. *Journal of the American Veterinary Medical Association* 1981; **178**: 1279–1282.
23. Hargis AM, Lee AC, Thomassen RW. Tumor and tumor-like lesions of perilimbal conjunctiva in laboratory dogs. *Journal of the American Veterinary Medical Association* 1978; **173**: 1185–1190.
24. Mughannam AJ, Hacker DV, Spangler WL. Conjunctival vascular tumors in six dogs. *Veterinary and Comparative Ophthalmology* 1997; **7**: 56–59.
25. Murphy CJ, Bellhorn RW, Buyukmihci NC. Bilateral conjunctival masses in two dogs. *Journal of the American Veterinary Medical Association* 1989; **195**: 225–228.
26. Peiffer RL Jr, Duncan J, Terrell T. Hemangioma of the nictitating membrane in a dog. *Journal of the American Veterinary Medical Association* 1978; **172**: 832–833.
27. Peiffer RL Jr, Terrell T. Episcleral hemangioma in a dog. *Journal of the American Veterinary Medical Association* 1978; **173**: 1338–1340.
28. Pirie CG, Knollinger AM, Thomas CB *et al.* Canine conjunctival hemangioma and hemangiosarcoma: a retrospective evaluation of 108 cases (1989–2004). *Veterinary Ophthalmology* 2006; **9**: 215–226.
29. Saunders LZ, Rubin LF. Neoplasms. In: *Ophthalmic Pathology of Animals*. S. Karger: Basel, 1975; 212–241.
30. Ferrer L, Fondevila D, Rabanal RM *et al.* Immunohistochemical detection of CD31 antigen in normal and neoplastic canine endothelial cells. *Journal of Comparative Pathology* 1995; **112**: 319–326.
31. Warren AL, Summers BA. Epithelioid variant of hemangioma and hemangiosarcoma in the dog, horse, and cow. *Veterinary Pathology* 2007; **44**: 15–24.
32. Chandler HL, Newkirk KM, Kusewitt DF *et al.* Immunohistochemical analysis of ocular hemangiomas and hemangiosarcomas in dogs. *Veterinary Ophthalmology* 2009; **12**: 83–90.
33. Donaldson D, Sansom J, Murphy S *et al.* Multiple limbal haemangiosarcomas in a border collie dog: management by lamellar keratectomy/sclerectomy and strontium-90 beta plesiotherapy. *Journal of Small Animal Practice* 2006; **47**: 545–549.
34. Liapis IK, Genovese L. Hemangiosarcoma of the third eyelid in a dog. *Veterinary Ophthalmology* 2004; **7**: 279–282.
35. Fife M, Blocker T, Fife T *et al.* Canine conjunctival mast cell tumors: a retrospective study. *Veterinary Ophthalmology* 2011; **14**: 153–160.
36. Barsotti G, Marchetti V, Abramo F. Primary conjunctival mast cell tumor in a Labrador Retriever. *Veterinary Ophthalmology* 2007; **10**: 60–64.
37. Hallstrom M. Mastocytoma in the third eyelid of a dog. *Journal of Small Animal Practice* 1970; **11**: 469–472.
38. Johnson BW, Brightman AH, Whiteley HE. Conjunctival mast cell tumors in two dogs. *Journal of the American Animal Hospital Association* 1988; **24**: 439–442.
39. Patnaik AK, Ehler WJ, MacEwen EG. Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs. *Veterinary Pathology* 1984; **21**: 469–474.
40. Kiupel M, Webster JD, Bailey KL *et al.* Proposal of a 2-tier histologic grading system for canine cutaneous mast cell tumors to more accurately predict biological behavior. *Veterinary Pathology* 2011; **48**: 147–155.
41. Wilcock B, Peiffer R Jr. Adenocarcinoma of the gland of the third eyelid in seven dogs. *Journal of the American Veterinary Medical Association* 1988; **193**: 1549–1550.
42. Donaldson D, Sansom J, Scase T *et al.* Canine limbal melanoma: 30 cases (1992–2004). Part 1. Signalment, clinical and histological features and pedigree analysis. *Veterinary Ophthalmology* 2006; **9**: 115–119.
43. Dees DD, Maclaren NE, Teixeira L *et al.* An unusual case of ocular melanosis and limbal melanocytoma with benign

intraorbital extension in a dog. *Veterinary Ophthalmology* 2012. doi: 10.1111/vop.12009. [Epub ahead of print].
44. Diters RW, Dubielzig RR, Aguirre GD *et al.* Primary ocular melanoma in dogs. *Veterinary Pathology* 1983; **20**: 379–395.
45. Giuliano EA, Chappell R, Fischer B *et al.* A matched observational study of canine survival with primary intraocular melanocytic neoplasia. *Veterinary Ophthalmology* 1999; **2**: 185–190.
46. Norman JC, Urbanz JL, Calvarese ST. Penetrating keratoscleroplasty and bimodal grafting for treatment of limbal melanocytoma in a dog. *Veterinary Ophthalmology* 2008; **11**: 340–345.
47. Ryan AM, Diters RW. Clinical and pathologic features of canine ocular melanomas. *Journal of the American Veterinary Medical Association* 1984; **184**: 60–67.
48. Wilcock BP, Peiffer RL Jr. Morphology and behavior of primary ocular melanomas in 91 dogs. *Veterinary Pathology* 1986; **23**: 418–424.
49. Donaldson D, Sansom J, Adams V. Canine limbal melanoma: 30 cases (1992–2004). Part 2. Treatment with lamellar resection and adjunctive strontium-90beta plesiotherapy–efficacy and morbidity. *Veterinary Ophthalmology* 2006; **9**: 179–185.
50. Featherstone HJ, Renwick P, Heinrich CL *et al.* Efficacy of lamellar resection, cryotherapy, and adjunctive grafting for the treatment of canine limbal melanoma. *Veterinary Ophthalmology* 2009; **12**(Suppl 1): 65–72.
51. Lewin GA. Repair of a full thickness corneoscleral defect in a German shepherd dog using porcine small intestinal submucosa. *Journal of Small Animal Practice* 1999; **40**: 340–342.
52. Wilkie DA, Wolf ED. Treatment of epibulbar melanocytoma in a dog, using full-thickness eyewall resection and synthetic graft. *Journal of the American Veterinary Medical Association* 1991; **198**: 1019–1022.
53. Sullivan TC, Nasisse MP, Davidson MG *et al.* Photocoagulation of limbal melanoma in dogs and cats: 15 cases (1989–1993). *Journal of the American Veterinary Medical Association* 1996; **208**: 891–894.
54. Dreyfus J, Schobert CS, Dubielzig RR. Superficial corneal squamous cell carcinoma occurring in dogs with chronic keratitis. *Veterinary Ophthalmology* 2011; **14**: 161–168.
55. Bernays ME, Flemming D, Peiffer RL Jr. Primary corneal papilloma and squamous cell carcinoma associated with pigmentary keratitis in four dogs. *Journal of the American Veterinary Medical Association* 1999; **214**: 215–217, 204.
56. Takiyama N, Terasaki E, Uechi M. Corneal squamous cell carcinoma in two dogs. *Veterinary Ophthalmology* 2010; **13**: 266–269.
57. Ward DA, Latimer KS, Askren RM. Squamous cell carcinoma of the corneoscleral limbus in a dog. *Journal of the American Veterinary Medical Association* 1992; **200**: 1503–1506.
58. Busse C, Sansom J, Dubielzig RR *et al.* Corneal squamous cell carcinoma in a Border Collie. *Veterinary Ophthalmology* 2008; **11**: 55–58.
59. Karasawa K, Matsuda H, Tanaka A. Superficial keratectomy and topical mitomycin C as therapy for a corneal squamous cell carcinoma in a dog. *Journal of Small Animal Practice* 2008; **49**: 208–210.
60. Latimer KS, Kaswan RL, Sundberg JP. Corneal squamous cell carcinoma in a dog. *Journal of the American Veterinary Medical Association* 1987; **190**: 1430–1432.
61. Montiani-Ferreira F, Kiupel M, Muzolon P *et al.* Corneal squamous cell carcinoma in a dog: a case report. *Veterinary Ophthalmology* 2008; **11**: 269–272.
62. Wiggans KT, Hoover CE, Ehrhart EJ *et al.* Malignant transformation of a putative eyelid papilloma to squamous cell carcinoma in a dog. *Veterinary Ophthalmology* 2012. doi: 10.1111/j.1463-5224.2012.01062.x. [Epub ahead of print].
63. Boscos CM, Ververidis HN, Tondis DK *et al.* Ocular involvement of transmissible venereal tumor in a dog. *Veterinary Ophthalmology* 1998; **1**: 167–170.
64. Grahn BH, Sandmeyer LS. Canine episcleritis, nodular episclerokeratitis, scleritis, and necrotic scleritis. *The Veterinary Clinics of North America Small Animal Practice* 2008; **38**: 291–308, vi.
65. Kircher CH, Garner FM, Robinson FR. Tumours of the eye and adnexa. *Bulletin of the World Health Organization* 1974; **50**: 135–142.
66. Labelle AL, Maddox CW, Daniels JB *et al.* Canine ocular onchocercosis in the united states is associated with Onchocerca lupi. *Veterinary Parasitology* 2013; **193**: 297–301.
67. Bussanich NM, Dolman PJ, Rootman J *et al.* Canine uveal melanomas: series and literature review. *Journal of the American Animal Hospital Association* 1987; **23**: 415–422.
68. Aguirre GD, Brown G, Shields JA *et al.* Melanoma of the choroid in a dog. *Journal of the American Animal Hospital Association* 1984; **20**: 471–476.
69. Collinson PN, Peiffer RL. Clinical presentation, morphology, and behavior of primary choroidl melanomas in eight dogs. *Progress Veterinary Comparative Ophthalmology* 1993; **3**: 158–164.
70. Dubielzig RR, Aguirre GD, Gross SL *et al.* Choroidal melanomas in dogs. *Veterinary Pathology* 1985; **22**: 582–585.
71. Hyman JA, Koch SA, Wilcock BP. Canine choroidal melanoma with metastases. *Veterinary Ophthalmology* 2002; **5**: 113–117.
72. Miwa Y, Matsunaga S, Kato K *et al.* Choroidal melanoma in a dog. *Journal of Veterinary Medical Science* 2005; **67**: 821–823.
73. Morgan RV, Patton CS. Choroidal melanoma in a dog. *The Cornell Veterinarian* 1993; **83**: 211–217.
74. Schoster JV, Dubielzig RR, Sullivan L. Choroidal melanoma in a dog. *Journal of the American Veterinary Medical Association* 1993; **203**: 89–91.
75. Trucksa RC, McLean IW, Quinn AJ. Intraocular canine melanocytic neoplasms. *Journal of the American Animal Hospital Association* 1985; **21**: 85–88.
76. Weisse I, Frese K, Meyer D. Benign melanoma of the choroid in a beagle: ophthalmological, light and electron microscopical investigations. *Veterinary Pathology* 1985; **22**: 586–591.
77. Paglia D, Dubielzig RR, Kado-Fong HK *et al.* Expression of cyclooxygenase-2 in canine uveal melanocytic neoplasms. *American Journal of Veterinary Research* 2009; **70**: 1284–1290.
78. Shimoyama Y, Akihara Y, Kirat D *et al.* Expression of monocarboxylate transporter 1 in oral and ocular canine melanocytic tumors. *Veterinary Pathology* 2007; **44**: 449–457.
79. Friedman DS, Miller L, Dubielzig RR. Malignant canine anterior uveal melanoma. *Veterinary Pathology* 1989; **26**: 523–525.
80. Galan A, Martin-Suarez EM, Molleda JM *et al.* Presumed primary uveal melanoma with brain extension in a dog. *Journal of Small Animal Practice* 2009; **50**: 306–310.
81. Michael SJ. Melanosarcoma of the eye with metastasis to the kidneys and ovaries. *Journal of the American Veterinary Medical Association* 1948; **113**: 253.
82. Minami T, Patnaik AK. Malignant anterior uveal melanoma with diffuse metastasis in a dog. *Journal of the American Veterinary Medical Association* 1992; **201**: 1894–1896.
83. Rovesti GL, Guandalini A, Peiffer R. Suspected latent vertebral metastasis of uveal melanoma in a dog: a case report. *Veterinary Ophthalmology* 2001; **4**: 75–77.

84. Steinmetz A, Ellenberger K, Marz I *et al.* Oculocardiac reflex in a dog caused by a choroidal melanoma with orbital extension. *Journal of the American Animal Hospital Association* 2012; **48**: 66–70.
85. Yi NY, Park SA, Park SW *et al.* Malignant ocular melanoma in a dog. *Journal of Veterinary Science* 2006; **7**: 89–90.
86. Pires I, Garcia A, Prada J *et al.* COX-1 and COX-2 expression in canine cutaneous, oral and ocular melanocytic tumours. *Journal of Comparative Pathology* 2010; **143**: 142–149.
87. Cook CS, Wilkie DA. Treatment of presumed iris melanoma in dogs by diode laser photocoagulation: 23 cases. *Veterinary Ophthalmology* 1999; **2**: 217–225.
88. Nasisse MP, Davidson MG, Olivero DK *et al.* Neodymium: YAG laser treatment of primary canine intraocular tumors. *Progress Veterinary Comparative Ophthalmology* 1993; **3**: 152–157.
89. Dietz HH, Jensen OA, Jorgensen JB. Malignant melanoma of the uvea in the dog. *Nordisk Veterinaermedicin* 1986; **38**: 68–73.
90. Esson D, Fahrer CS, Zarfoss MK *et al.* Suspected uveal metastasis of a nail bed melanoma in a dog. *Veterinary Ophthalmology* 2007; **10**: 262–266.
91. Petersen-Jones SM, Forcier J, Mentzer AL. Ocular melanosis in the Cairn Terrier: clinical description and investigation of mode of inheritance. *Veterinary Ophthalmology* 2007; **10**(Suppl 1): 63–69.
92. Petersen-Jones SM, Mentzer AL, Dubielzig RR *et al.* Ocular melanosis in the Cairn Terrier: histopathological description of the condition, and immunohistological and ultrastructural characterization of the characteristic pigment-laden cells. *Veterinary Ophthalmology* 2008; **11**: 260–268.
93. van de Sandt RR, Boeve MH, Stades FC *et al.* Abnormal ocular pigment deposition and glaucoma in the dog. *Veterinary Ophthalmology* 2003; **6**: 273–278.
94. Peiffer RL Jr. Ciliary body epithelial tumours in the dog and cat; a report of thirteen cases. *Journal of Small Animal Practice* 1983; **24**: 347–370.
95. Dubielzig RR, Steinberg H, Garvin H *et al.* Iridociliary epithelial tumors in 100 dogs and 17 cats: a morphological study. *Veterinary Ophthalmology* 1998; **1**: 223–231.
96. Whittemore JC, Gionfriddo JR, Steyn PF *et al.* Indium-111 labeled vitamin B12 imaging of a ciliary adenoma with concurrent grade 2 soft tissue sarcoma of the leg in a Labrador Retriever. *Veterinary Ophthalmology* 2004; **7**: 209–212.
97. Klosterman E, Colitz CM, Chandler HL *et al.* Immunohistochemical properties of ocular adenomas, adenocarcinomas and medulloepitheliomas. *Veterinary Ophthalmology* 2006; **9**: 387–394.
98. Labelle P, Reilly CM, Naydan DK *et al.* Immunohistochemical characteristics of normal canine eyes. *Veterinary Pathology* 2012; **49**: 860–869.
99. Hendrix DV, Donnell RL. Lenticular invasion by a ciliary body adenocarcinoma in a dog. *Veterinary Pathology* 2007; **44**: 540–542.
100. Zarfoss MK, Dubielzig RR. Metastatic iridociliary adenocarcinoma in a labrador retriever. *Veterinary Pathology* 2007; **44**: 672–676.
101. Clerc B. Surgery and chemotherapy for the treatment of adenocarcinoma of the iris and ciliary body in five dogs. *Veterinary and Comparative Ophthalmology* 1996; **6**: 265–270.
102. Aleksandersen M, Bjerkas E, Heiene R *et al.* Malignant teratoid medulloepithelioma with brain and kidney involvement in a dog. *Veterinary Ophthalmology* 2004; **7**: 407–411.
103. Lahav M, Albert DM, Kircher CH *et al.* Malignant teratoid medulloepithelioma in a dog. *Veterinary Pathology* 1976; **13**: 11–16.
104. Langloss JM, Zimmerman LE, Krehibiel JD. Malignant intraocular teratoid medulloepithelioma in three dogs. *Veterinary Pathology* 1976; **13**: 343–352.
105. Wilcock B, Williams MM. Malignant intraocular medulloepithelioma in a dog. *Journal of the American Animal Hospital Association* 1980; **16**: 617–619.
106. Duke FD, Brudenall DK, Scott EM *et al.* Metastatic uveal schwannoma of blue-eyed dogs. *Veterinary Ophthalmology* 2013. doi: 10.1111/vop.12022. [Epub ahead of print].
107. Olbertz L, Langohr I, Werner J *et al.* Anterior uveal spindle cell tumor in a blue-eyed mixed-breed dog. *Veterinary Ophthalmology* 2013. doi: 10.1111/vop.12018. [Epub ahead of print].
108. Zarfoss MK, Klauss G, Newkirk K *et al.* Uveal spindle cell tumor of blue-eyed dogs: an immunohistochemical study. *Veterinary Pathology* 2007; **44**: 276–284.
109. Sato T, Yamamoto A, Shibuya H *et al.* Intraocular peripheral nerve sheath tumor in a dog. *Veterinary Ophthalmology* 2005; **8**: 283–286.
110. Ladds PW, Gelatt KN, Strafuss AC *et al.* Canine ocular adenocarcinoma of mammary origin. *Journal of the American Veterinary Medical Association* 1970; **156**: 63–69.
111. Naranjo C, Dubielzig RR, Friedrichs KR. Canine ocular histiocytic sarcoma. *Veterinary Ophthalmology* 2007; **10**: 179–185.
112. Render JA, Carlton WW, Vestre WA *et al.* Osteosarcoma metastatic to the globes in a dog. *Veterinary Pathology* 1982; **19**: 323–326.
113. Szymanski CM. Bilateral metastic intraocular hemangiosarcoma in a dog. *Journal of the American Veterinary Medical Association* 1972; **161**: 803–805.
114. Naranjo C, Schobert C, Dubielzig R. Canine ocular gliomas: a retrospective study. *Veterinary Ophthalmology* 2008; **11**: 356–362.
115. Caswell J, Curtis C, Gibbs B. Astrocytoma arising at the optic disc in a dog. *Canadian Veterinary Journal* 1999; **40**: 427–428.
116. Meyerholz DK, Haynes JS. Solitary retinal astrocytoma in a dog. *Veterinary Pathology* 2004; **41**: 177–178.
117. Spiess BM, Wilcock BP. Glioma of the optic nerve with intraocular and intracranial involvement in a dog. *Journal of Comparative Pathology* 1987; **97**: 79–84.
118. Mauldin EA, Deehr AJ, Hertzke D *et al.* Canine orbital meningiomas: a review of 22 cases. *Veterinary Ophthalmology* 2000; **3**: 11–16.
119. Buyukmihci N. Orbital meningioma with intraocular invasion in a dog Histology and ultrastructure. *Veterinary Pathology* 1977; **14**: 521–523.
120. Perez V, Vidal E, Gonzalez N *et al.* Orbital meningioma with a granular cell component in a dog, with extracranial metastasis. *Journal of Comparative Pathology* 2005; **133**: 212–217.
121. Regan DP, Kent M, Mathes R *et al.* Clinicopathologic findings in a dog with a retrobulbar meningioma. *Journal of Veterinary Diagnostic Investigation* 2011; **23**: 857–862.
122. Montoliu P, Anor S, Vidal E *et al.* Histological and immunohistochemical study of 30 cases of canine meningioma. *Journal of Comparative Pathology* 2006; **135**: 200–207.
123. Headrick JF, Bentley E, Dubielzig RR. Canine lobular orbital adenoma: a report of 15 cases with distinctive features. *Veterinary Ophthalmology* 2004; **7**: 47–51.
124. Attali-Soussay K, Jegou JP, Clerc B. Retrobulbar tumors in dogs and cats: 25 cases. *Veterinary Ophthalmology* 2001; **4**: 19–27.
125. Hendrix DV, Gelatt KN. Diagnosis, treatment and outcome of orbital neoplasia in dogs: a retrospective study of 44 cases. *Journal of Small Animal Practice* 2000; **41**: 105–108.
126. Kern TJ. Orbital neoplasia in 23 dogs. *Journal of the American Veterinary Medical Association* 1985; **186**: 489–491.