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PROGNOSTIC FACTORS FOR VETERINARY ONCOLOGY

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When discussing treatment options for pets with cancer, veterinarians are invariably asked to provide information regarding prognosis. Knowledge and accurate interpretation of the most recent literature and research findings are essential for providing clients with prognostic information that will guide them through difficult treatment decisions. Because veterinary oncology is such a dynamic specialty, new information is added to the literature every month. This review is intended to provide a current basis for discussions of prognosis. Tumours encountered on a regular basis or for which recent updates regarding prognostic variables are available will be reviewed.

Apocrine gland anal sac adenocarcinoma (AGASACA)

In a retrospective study comprised of 80 cases of AGASACA diagnosed between 1996 and 2003, Polton and Brearley identified four statistically significant negative prognostic factors, namely: primary tumour size > 2.5 cm, presence of lymph node metastases, presence of distant metastatic disease, and lack of therapy. They then used these prognostic factors to develop a clinical staging system and case management algorithm which they tested prospectively in 50 affected dogs. This new staging system proved to be relevant to case management, with survival time significantly associated with clinical stage in both the retrospective and prospective evaluation. The staging scheme proposed by Polton, et al. is as follows:

Clinical Stage	T	N	M
1	< 2.5 cm	None	None
2	> 2.5 cm	None	None
3a	Any T	Present; < 4.5 cm	None
3b	Any T	Present; > 4.5 cm	None
4	Any T	Any N	Present

In contrast to this report and a 2003 report by Williams, et al, a study by Emms did not indicate a significant difference in outcome for dogs with lymph node metastases, compared to those without. All three reports suggested a role for surgery in improving the prognosis for affected dogs and the reports by Emms and Polton suggest there is a role for chemotherapy in conjunction with cytoreductive surgery for this disease.

Mammary tumours

Whereas most feline mammary tumours are malignant, approximately 50% of all canine mammary tumours (CMT) are benign. Of the malignant lesions, those that are high-grade or poorly differentiated carry a poorer prognosis. Inflammatory mammary carcinoma and mammary sarcomas are the most aggressive CMT, with affected dogs rarely surviving one year. One report suggests that ductal carcinomas also warrant a poorer prognosis than other mammary carcinomas. In cats, tumour size is the most important prognostic factor. Median survival time (MST) for cats with 3-cm or larger tumours was 12 months, compared to 21 months for cats with smaller tumours in one

study. Small tumour size (< 3 cm) also warrants a more favourable prognosis in dogs, provided invasion of the lymphatics has not occurred. In one report, dogs whose tumours invaded lymphatics or blood vessels had a 97% recurrence or metastatic rate at two years compared 19% in dogs with tumours limited to the mammary duct system. Nodal metastasis may also indicate a greater likelihood of tumour recurrence. Presence of lymphoid cellular reactivity around the tumour has been associated with a better prognosis in dogs, likely because it indicates an immune response against the tumour. Recurrence rates are almost twice as high for Grade I tumours that lack this reactivity. Other reported prognostic factors that negatively impact clinical outcome for dogs are tumour ulceration, DNA ploidy, increased S-phase activity, lack of hormone receptor activity, and obesity. In dogs, tumour location and number are not prognostic, nor is the type of surgery used to excise them, provided it results in a complete excision. Chemotherapy may affect prognosis, although reports are scarce. In one small (n=16) prospective study comparing outcome for dogs with high-risk disease (Stage III or IV) treated with surgery only to those undergoing surgery and adjuvant chemotherapy (5-FU and cyclosphosphamide), the chemotherapy group fared considerably better (24 month MST vs. 6 months). Further prospective evaluations are needed to clarify the role of chemotherapy for this disease in dogs. The same can be said for feline mammary cancer**.** In a recent randomized prospective study by the author and others, outcome was compared between cats receiving mitoxantrone chemotherapy and those receiving doxorubicin after unilateral or bilateral mastectomy for mammary carcinoma. Surgery type and the choice of chemotherapy agent were not prognostic for outcome, with an overall MST of 940 days.

Oral tumours

See “Oral Tumours” lecture by the same author for more information. The table below provides a brief summary of some of the prognostic factors for canine oral tumours:

Tumour	Prognostic Factors	Details
Melanoma	Tumour Size and Stage	<2 cm better
	Surgery	Successful first surgery warrants better prognosis
	Nuclear atypia - based on incremental score from 1 to 10	More atypia = worse prognosis
SCC	Location	Rostral
	Size	For those treated with radiation: <2 cm , PFI >68 months 2 to 4 cm, PFI =28 months > 4 cm, PFI = 8 months
FSA	Location and surgical margins	Rostral better; tumour-free margins associated with improved outcome

Soft tissue sarcomas

Of the known prognostic factors for STS, mitotic index and histological grade are perhaps the best established. In 1997 Kuntz, et. al. reported a grading system defining

STS as Grade I, II, or III based on degree of differentiation, number of mitoses, and amount of tumour necrosis. Metastatic rates of STS correlated well with this grading scheme. Roughly 10% of Grade I tumours metastasize, compared to ~ 20% of Grade II and ~50% of Grade III tumours Mitotic index (MI), or the number of mitoses per ten high power fields, has been shown in at least two studies to be prognostic. In the Kuntz study, dogs with a tumour MI >19 had a MST of 236 days, compared to 532 days with a MI of 10 to 19 and 1444 days with a MI <10. Tumour size <5cm, superficial or extremity location, mobility, and tumour-free surgical margins are reported to be positive prognostic factors for STS in dogs. Even when margins are not tumour-free, adjuvant radiation therapy may provide a favourable prognosis, with reported 5-year survival rates in excess of 75%. In a recent paper by Selting, et al, the addition of doxorubicin to the treatment protocol did not significantly improve prognosis for dogs with STS.

Canine mast cell tumours

Histopathological grade using the Patnaik scheme is one of the best established predictors of canine mast cell tumour (MCT) behaviour. The grading scheme was shown to correlate well with 1500-day survival rates in the original study (Grade I = 83%, Grade II = 44%, and Grade III = 6%). Argyrophilic nucleolar organizer region (AgNOR) counts may be performed on both cytological and histological preparations and are also of prognostic significance. Higher counts correlate with higher histopathologic grade and poorer prognosis. Cost of preparation and the expertise required for interpretation have limited the popularity of this staining procedure. Other negative prognostic factors for canine MCT include clinical stage > Stage 1, rapid tumour growth, tumour-associated systemic illness, abnormal chromosome number in tumour cells, and a history of MCT recurrence. Mast cell tumours in Boxers are reportedly associated with a more favourable prognosis for survival. New molecular markers are being evaluated to determine their prognostic value for MCT and the tumour grading system is undergoing review. Some tumour locations once thought to warrant a poor prognosis (perineum and inguinal area) have been re-evaluated and found not to have prognostic significance. Other tumour sites including the muzzle and ear are thought to warrant a poor prognosis, although the latter association has not been published in the peer-reviewed literature to date and, therefore, cannot be considered to be an established prognostic factor. Recent work by Thamm, et al. suggests that mucocutaneous location warrants a poor prognosis. The same study suggests that prophylactic nodal irradiation improves prognosis for dogs with MCT.

Lymphoma

The WHO staging system for canine lymphoma provides some prognostic information, although reports vary. While most would agree that dogs presenting with Stage I and II disease have a better prognosis than dogs with Stage V lymphoma, the relationship of Stage III or IV disease to prognosis, compared to other stages is less clear. Dogs that are clinically ill (substage b) have a poorer prognosis than those without systemic illness (substage a). Medium to high grade tumours generally respond well to initial therapy, but survival times are shorter than with low-grade tumours. Immunophenotype is of prognostic value in that T-cell tumours generally warrant a poorer prognosis than do B-cell tumours. Tumour sites associated with a poorer prognosis include the skin,

gastrointestinal tract, and bone marrow. Additional negative prognostic factors include male gender, hypercalcaemia and previous corticosteroid therapy. Smaller dogs (<15 kg) are reported to have a better prognosis, but this likely relates to the fact that chemotherapy drug dosing on a m^2 basis provides a relatively larger area under the curve for the drugs in small dogs. The current veterinary classification of lymphoma is rudimentary at best, compared to the schemes used in human medicine. As we improve our recognition of lymphoma subclassifications and syndromes, we will likely improve our ability to provide a more accurate prognosis. A newly recognized syndrome in cats in the US is cutaneous lymphoma overlying the tarsus, often in FIV positive cats. Prognostic significance of this particular presentation is unclear at this time. In general, cats with nasal lymphoma have the best prognosis and young FeLV+ cats with mediastinal lymphoma have the worst. Reported positive prognostic factors for cats are negative FeLV status, early clinical stage, and use of doxorubicin chemotherapy.

Primary lung tumours

Adenocarcinoma (ACA) is the most common canine primary lung tumour and warrants a better prognosis than the less common squamous cell carcinoma (SCC). This is because SCC tends to be diffuse at the time of diagnosis. Other poor prognostic indicators include tumour size > 100 cm^3 or 2 inches, lymph node metastasis, and pleural effusion. Of these factors, lymph node involvement is the most significant, with a marked survival advantage reported for dogs lacking nodal metastasis (12-month MST vs. 60-day for those with nodal metastasis). Dogs with tumours located in the periphery of the lung parenchyma fare better than those with tumours involving an entire lobe.

Nasal tumours

One difficult aspect of data interpretation as it relates to the literature regarding canine nasal tumours is that the majority of published reports include multiple different tumour types. As such, it is hard to discern prognostic factors for this disease. What does seem clear from published reports is that metastatic disease at the time of diagnosis warrants a poor prognosis. In a report limited to nasal ACA, the author and others demonstrated that degree of local invasion was not of prognostic value, whereas the presence of metastasis was. At least two studies have shown a survival advantage for dogs with sarcomas vs. carcinomas, although this is still an issue of debate. Nasal ACA reportedly responds better to radiation than SCC and poorly differentiated carcinoma. In a report of 139 dogs with untreated nasal carcinoma, Rassnick, et al found epistaxis to be the only risk factor significantly associated with survival. Dogs presenting with epistaxis had a MST of 88 days, compared to 224 days for dog without epistaxis.

Osteosarcoma

See “Osteosarcoma in Dogs” lecture by the same author for more information. Briefly, the factors reported to be associated with a poor prognosis for canine appendicular OSA include young age (<5 years), high presurgical values of total alkaline phosphatase and bone-specific alkaline phosphatase, proximal humeral site, large tumour size and nodal or gross distant metastatic disease at the time of diagnosis. For OSA of the flat or irregular bones, higher body weight, telangiectatic subtype, incomplete excision, and rib or scapular location are identified as negative prognostic factors, whereas mandibular OSA is associated with a more favourable prognosis.

REFERENCES AVAILABLE UPON REQUEST FROM THE AUTHOR