Canine cutaneous MCTs
Mast cell tumors (MCTs) are the most commonly diagnosed malignant skin tumors in dogs. While canine cutaneous MCTs (cMCTs) rarely pose a diagnostic challenge (as most can be diagnosed cytologically), distinguishing cMCTs with a potentially benign vs malignant biologic behavior can be difficult. We will review the current state of diagnostics and prognostication of canine cMCTs and discuss how a combined approach, based on clinical and pathologic assessment, is important in local and systemic treatment recommendations.

The most important and widely used pathologic assessment is histologic grading. The accepted grading schemes are the 3-tier Patnaik and 2-tier Kiupel systems. Most pathologists will apply both grading systems to all cMCTs. The Patnaik system designates cMCTs as grade I, II, or III based on depth of invasion, cellular atypia, granularity, nuclear features, mitotic count and multinucleation. The Kiupel system designates cMCTs as low or high-grade based on mitotic count, presence of multinucleation, bizarre nuclei and karyomegaly. In general, the two-tier system has superior inter-observer consistency and is superior in identifying those dogs that will require additional therapy beyond surgical excision. Approximately 90% of cMCTs are low grade. Of the 10% of dogs with high grade cMCTs, it is estimated that 90% will die due to MCT-associated disease; only 5% of dogs with low grade cMCTs will die from MCT-associated disease. Mitotic count is predictive of outcome independent of tumor grade. A newer study also proposes a cytologic grading scheme for canine cMCTs. The cytologic grading scheme that best correlated with histology classified a tumor as high grade if it was poorly granulated or had at least 2 of the following features: presence of mitotic figures, binucleated or multinucleated cells, nuclear pleomorphism, or >50% anisokaryosis. Dogs assigned a high grade on FNA/cytology were 25 times more likely to die within 2 years. While cytologic grading is not currently widely applied by clinical pathologists, if features of a high grade MCT are present, owners may be counseled about concerns for potential aggressive biologic behavior.

Markers of proliferation (particularly AgNORs and Ki67) as well as KIT localization and mutation status have been evaluated to assist in determining whether a MCT is likely to behave in a more aggressive manner; these features can be assessed on biopsy samples through most commercial laboratories as part of a MCT prognostic panel. There are several situations in which this type of testing can be helpful. An example is testing low-grade tumors (Kiupel system) that are marginally or incompletely excised, as Ki67 and AgNOR values help predict the
likelihood of tumor regrowth in this setting. Incomplete low grade MCTs with low AgNOR x Ki67 score are highly unlikely to recur despite incomplete surgical margins whereas those with high scores are likely to recur (therefore further warranting further therapy). The panel can also aid in predicting behavior of MCTs that are intermediate in histologic appearance or have conflicting microscopic characteristics (such as low mitotic count but bizarre nuclei and multinucleation). MCT with an identified c-kit mutation may be preferentially treated with tyrosine kinase inhibitors (toceranib).

**Evaluation of tumor margins** is an important part of assessing excised cMCTs but can be challenging. Recurrence of MCT following surgical excision has been associated with a more guarded prognosis. Additionally, up to 40% of high grade MCT will recur in spite of complete/wide histologic margins.

There are several **miscellaneous factors** associated with prognosis in dogs with cMCTs. Certain breeds of dogs such as Boxers, pugs and dogs of bulldog descent develop MCTs that often behave in a more benign fashion whereas Shar-Peis have a predilection for high grade tumors. Tumors in the preputial, scrotal, subungual, oral and muzzle sites have been linked to an aggressive behavior. Conjunctival MCT most commonly have a good prognosis as do MCT classified as subcutaneous in nature. Recent rapid growth and tumor ulceration have been associated with a worse outcome. MCT measuring >3cm in diameter are associated with increased risk of regional lymph node metastasis. Systemic signs of illness including anorexia, vomiting, melena and edema are associated with visceral metastasis and poor prognosis.

While **staging** is an important prognostic tool for cMCTs, methods of staging and interpretation of histologic or cytologic samples of lymph nodes or visceral organs are not free from controversy. In general, evaluation of local lymph node(s) should be performed in every dog with MCT diagnosis if accessible given that local lymph nodes are the most common initial site of metastasis. A more recent study found the presence of histologically detectable metastatic disease in nearly half of dogs undergoing extirpation of non-palpable/normal-sized regional lymph nodes as part of staging of cMCT. Abdominal ultrasound with routine spleen +/- liver aspiration should be performed regardless of ultrasonographic appearance in dogs with a clinically aggressive mast cell tumor or those showing signs of systemic illness.

**Treatment** options for cMCTs includes both local therapy as well as systemic therapy. Treatment decisions are predicated on the presence or absence of negative prognostic factors and on the clinical stage of disease. Local options include surgery, radiation therapy and intralesional corticosteroids. Systemic options include oral corticosteroids, chemotherapy (conventional agents as well targeted agents) and supportive medications. These options are briefly reviewed.

The initial recommended treatment for most cMCT is wide **surgical excision**. For tumors with a large amount of peri-tumoral edema, neoadjuvant prednisone (1mg/kg day, tapering) may help to aid in better defining tumor margins (70% response rates reported in terms of reduction in tumor size or edema). Most studies support obtaining a wide margin (1-3cm lateral margin and 1 fascial plane deep). **Radiation therapy** can be used in the adjuvant setting (to “clean up” residual disease after incomplete excision) or in the setting of inoperable tumors (either palliative protocol or stereotactic radiosurgery). **Intralesional triamcinolone** treatment can provide short-
term (median of 2 months) tumor control/palliation (response rate of 70%). **Chemotherapy** treatment can be used in the setting of gross disease (non-resectable or recurrent tumors, multiple MCTs, advanced stage disease) or in the adjuvant/post-operative setting for tumors with an aggressive biologic behavior. Conventional chemotherapy protocols used most commonly are vinblastine + prednisone (weekly treatments for 4 weeks, then every other week for 4 treatments), lomustine and prednisone (treatments every 3 weeks for 4 to 6 cycles), and chlorambucil + prednisone (daily or every other day long-term). Receptor tyrosine kinase inhibitors, most notably **toceranib (Palladia)**, can also play an important role in the management of cMCTs. The overall biologic response rate for dogs with MCT undergoing Palladia treatment is 60% when compared to 80% for dogs with a documented c-kit mutation. Therefore, it is not necessary for a MCT to have a c-kit mutation in order for there to be a potential therapeutic benefit from the medication. Palladia treatment is typically administered on an every-other day or MWF schedule and can be combined with prednisone, palliative radiation or other chemotherapy agents (such as vinblastine and lomustine). Neutropenia is the dose-limiting toxicity when combined with other chemotherapeutic agents. Typically, Palladia treatment is continued for a minimum of 6 months (in the setting in which a complete remission is achieved) or as long as effective in aiding in tumor control (in the gross disease setting).

**Feline MCTs**  
Unlike MCTs in dogs, which predominantly arise from cutaneous/subcutaneous tissues, MCTs in cats typically arise from three distinct anatomic locations: cutaneous, splenic/visceral, and intestinal sites, although multiple organ systems may be involved at one time.

Cutaneous MCTs (cMCTs) account for approximately 20% of feline skin tumors and represent the second most common skin tumor in cats (basal cell tumors are most common). Although the typical presentation is a benign tumor that can be cured by narrow surgical excision, a small but important percentage (up to 25%) of feline cMCTs are biologically aggressive and can spread to locoregional lymph nodes, precede the onset of disseminated cutaneous tumors, or be associated with visceral involvement. Prognosis was previously difficult to estimate as unlike canine cMCTs, there was no grading system developed for feline cMCTs. However, a basic grading system has recently been developed that aids in identification of feline cMCTs with an aggressive biologic behavior. According to this scheme, high grade tumor classification requires >5 mitotic figures in 10hpf and at least 2 of the following criteria: tumor diameter > 1.5cm, irregular nuclear shape, and nucleolar prominence/chromatin clusters. According to this scheme, high-grade cMCTs were associated with significantly reduced MST (349 days) as compared with the low-grade tumors (MST not reached).

MCTs represent up to 1/4 of all splenic disease in cats. Anemia is the most common hematologic finding and up to 1/3 of cats have abdominal or pleural effusions that are cytologically diagnostic (eosinophil and mast cell rich). Splenectomy is the treatment of choice for feline splenic MCT, **even for cats with systemic involvement**. Reported MST varies based on study (13 to 28 months). The role of chemotherapy in this disease process has not been fully elucidated, but chemotherapy is indicated if there is evidence of disease progression/relapse (such as new sites of disease) or lack or resolution of mastocytosis or cMCTs over the course of a few months (for cats with more systemic disease involvement) following splenectomy.
Intestinal MCT is the third most common primary intestinal tumor in cats (after lymphoma and adenocarcinoma). Intestinal MCT most commonly affects the small intestine, typically appearing as a focal, non-circumferential, eccentric mass on abdominal ultrasound. However, lesions can be multi-focal in nature. Mesenteric lymph node metastasis is common as is hepatosplenic involvement. Fine needle aspirate and cytology is typically diagnostic; however, cytoplasmic granules may be less prominent when compared to the other anatomic forms of feline MCT. While intestinal MCT has historically been associated with a poor prognosis (MST of weeks to a few months), there are recent studies with more promising overall MST of >1 year, which includes cats treated with glucocorticoids as a single agent. Treatment options include surgery (if a focal mass) +/- systemic chemotherapy +/- glucocorticoids.

In general, chemotherapy treatment is indicated in cases of high-grade cutaneous MCT. The medications with the greatest anti-tumor activity for feline MCT are chlorambucil and lomustine as well as the tyrosine kinase inhibitor toceranib (Palladia). Unique side effects to note about these drugs in cats are the possibility for a delayed nadir with lomustine (which can necessitate treatments every 6 weeks) and hepatotoxicity with toceranib (which manifests as an acute liver enzyme elevation and requires permanent discontinuation of the medication). For chemotherapy medications administered at home, it is critical that owners are educated about safe medication handling practices. Glucocorticoids appear to have the greatest clinical benefit in cats with the gastrointestinal form of the disease.

References available upon request.