Mast cell tumors are one of the most common cutaneous tumors in the dog. Biologic behavior is variable and clinical outcome is best predicted by histologic grade. Grade I tumors are usually well differentiated, rarely metastasize and are associated with an excellent outcome. Grade II tumors are locally invasive, may spread to local lymph nodes, and uncommonly spread throughout the body. A population of intermediate grade (Patnaik grade II) MCTs appear to follow a more malignant course, spreading locally and to distant sites. Additional factors are often considered in attempt to predict the behavior of grade II tumors. Grade III tumors are usually anaplastic and locally aggressive, with a high rate of metastasis. These tumors are not cured typically, but many dogs can have extended remissions if tumors are caught early and treated aggressively. In practice, deciphering which MCTs will behave aggressively can be difficult, making prognosis and optimal treatment challenging to predict. Consideration of a number of clinical (tumor size, clinical signs, etc.) and histologic factors (mitotic index, c-kit, etc.) can be used to help the clinician best present to and guide clients through a wide range of diagnostic and treatment options.

Diagnosis and staging
In most cases, MCTs can be easily diagnosed via fine needle aspirate and cytology with the rapid hematologic-type stains used in most practices. A small percentage of MCTs may have poorly staining granules, in which case a Wright-Giemsa or toluidine blue stain may be necessary. If histopathology is required for diagnosis, careful consideration of tumor location, size, and clinical factors is needed to plan for biopsy. When possible, wide excisional biopsy is preferred and incisional biopsy is uncommonly pursued in the author’s practice.

Staging is important in the clinical evaluation of canine MCT patients; however, what constitutes adequate staging is controversial. In select cases, an extensive work-up may not be necessary. Generally speaking, a minimum database (complete blood count serum biochemistry profile) and regional lymph node cytology are recommended for all dogs with MCT. These diagnostics are typically inexpensive and quick to perform and are likely sufficient for cases where the tumor is amenable to wide surgical excision and no negative prognostic factors are present. Histologic assessment of a regional lymph node may be required for definitive diagnosis of regional metastasis if cytology is suspicious but not definitive for metastatic disease. If the tumor is in an undesirable surgical location or if negative prognostic factors exist, further staging with abdominal ultrasound is advised. Abdominal ultrasound is non-invasive and allows evaluation of spleen, liver, and intra-abdominal lymph nodes for metastatic disease. Fine needle aspirate of the spleen and liver are always advised if the organs look abnormal. Several studies have suggested that FNA of the spleen and liver is warranted in the case of clinically or histopathologically aggressive disease even if they appear normal on ultrasound. In the author’s practice, splenic aspirate is strongly advised for any high grade II or III tumor or in the case of concerning clinical behavior (see prognostic factors). Thoracic radiographs rarely reveal metastasis. However, it is reasonable to pursue this as a pre-anesthetic screening and to rule out other unrelated disease processes prior to a surgical procedure. Bone marrow aspirate is rarely indicated.

Prognostic factors
Grade
Histologic grade is considered the most consistent prognostic factor available for canine MCT but should be interpreted in light of other prognostic factors when making treatment decisions. Histopathologic grading is complicated by inter-observer variation among pathologists. Currently, two forms of grading are reported in clinical practice. The most commonly utilized grading system is the Patnaik grading system (low- grade I, intermediate- grade II, high- grade III). More recently, a 2-tier histologic grading system (low, high) has been introduced for canine MCTs. The second system was developed in an attempt to compensate for some of the weaknesses of the Patnaik system. However, further validation is needed to determine if this is truly better at predicting behavior and clinical outcome.

Proliferation indices
Mitotic index (MI) is a strong predictor of overall survival in dogs. Using a cutoff of 5/10 high powered fields, dogs with a low MI (<5) had a median survival time of 80 months compared to 3 months for dogs with a high MI (>5). It is advisable that any tumor with a high MI is staged and treated as an aggressive MCT in practice.
Other markers of proliferation that have been evaluated include Ki67 (a protein in the nucleus that correlates with cell proliferation), AGNORs (argyrophilic nuclear organizer regions), and PCNA. These require the use of special stains and are often included in the MCT prognostic panel. Interpretation of this panel can often be confusing for clinicians. At this point, it appears that Ki67 is most useful clinically as a prognostic factor for intermediate grade tumors to help predict expected survival times when the clinical picture remains confusing based on other factors.

C-Kit

KIT (a receptor tyrosine kinase) dysregulation has been implicated in the pathogenesis of MCT development and evaluated as a prognostic factor. While KIT staining patterns (cytoplasmic localization) may be associated with dysregulation and prognosis, clinical application of this as a prognostic factor remains challenging. Alternatively, the presence of c-kit activating mutations is strongly associated with a higher rate of local recurrence, metastasis, and death from disease and should be considered a poor prognostic indicator.

Tumor location

Some tumor locations may differ in behavior and prognosis. Subcutaneous tumors may have a better prognosis. Mucous membrane sites, subungual, and visceral tumors are associated with a worse prognosis. Conjunctival tumors and those of the eyelid margin may be an exception with studies showing prolonged survival after surgery alone. Perioral and muzzle MCTs have an increased risk of locoregional metastasis yet prolonged median survival times despite the higher rate of lymph node metastasis. Scrotal and preputial tumors may be associated with a worse prognosis but this remains controversial.

Clinical stage

Higher stage disease is associated with a worse prognosis. The effect of lymph node metastasis on outcome may be dependent on grade of the primary tumor and how the lymph node is treated. Thus, clinical judgment is important. Multiple tumors may not negatively affect prognosis.

Other factors

Local recurrence, systemic and local clinical signs, growth rate, and tumor size have all been correlated with prognosis and should be considered in the overall evaluation of a patient’s tumor.

Treatment options

Primary therapy

Wide surgical excision is the primary treatment of choice for tumors localized to the skin and subcutaneous tissues. Adequate tissue margins may be related to grade; however, grade is often unknown prior to therapy. At least 2-3 cm lateral margins and one tissue plane deep is generally recommended; 2 cm margins are likely adequate for grade I and II tumors. One study found no local recurrence at 2 years for primarily low to intermediate grade tumors removed with a lateral histologic margin of >10 mm and a deep histologic margin of >4 mm. However, histologic margin size may not accurately reflect margin size at surgery. Histopathology is advised for every tumor to determine grade and evaluate margins. The majority of low and intermediate grade tumors are cured with adequate surgical excision. Occasionally, external beam radiation therapy (RT) may be used as a primary treatment in cases of non-resectable tumors. Approaching the dog with multiple mast cell tumors can be challenging and primary therapy should be considered on a case by case basis.

Adjuvant local therapy

Adjuvant local therapy should be discussed with pet owners when adequate margins cannot be achieved due to location or histologic assessment reveals incomplete or narrow excision. Unfortunately, confusion exists regarding which tumors require additional treatment due to varied reports of local recurrence rate in incompletely and narrowly resected tumors (ranging anywhere from about 12-60%). When local therapy is being considered, grade, proliferation indices and c-kit status may be helpful in determining which cases would benefit. The implication of regrowth based on location may also play a factor in discussion with owners regarding the importance of adjuvant therapy. Standard of care options include primary re-excision and radiation therapy, both of which have been found to reduce local recurrence rates and increase survival times. MCTs are radiosensitive and 75-96% of dogs will have a local cure with adjuvant radiation therapy. An alternative option is electrochemotherapy (when available) which shows initial promise in improving local control for incompletely removed tumors.

Systemic therapy

Chemotherapy or tyrosine kinase inhibitors (TKIs) should be offered following excision of tumors in dogs with poor prognostic indicators (grade III, high mitotic index, metastasis, poor location, etc.). High grade and metastatic mast cell tumors are unlikely to be cured, but adjuvant therapy may improve disease free intervals and survival times. Vinblastine and lomustine are commonly used traditional chemotherapy agents. Response rates range from 11-64% when used against bulky disease; however, chemotherapy is more successful against microscopic disease. A variety of chemotherapy protocols exist. A combination vinblastine/prednisone protocol is preferred as a first-line protocol for adjuvant therapy in the author’s practice (weekly therapy for 4 treatments and then biweekly therapy for 4 treatments). If the initial vinblastine dose is well tolerated (2 mg/m2), dose escalations (increases of 0.25 mg/m2 at a time up to 3.5 mg/m2) should be considered in an attempt to improve efficacy. Lomustine (CCNU) is typically dosed every 2-3 weeks.
and requires close monitoring due to potential for myelosuppression and hepatotoxicity. Denamarin is recommended as supportive therapy for any dog treated with lomustine. Paclitaxel (Paccal Vet) has also recently been evaluated and appears to be safe and clinically effective for gross disease (complete or partial response 59%). However, the role of this agent in the adjuvant setting has not yet been defined. Metronomic chlorambucil may also be a consideration in cases where dogs have failed other therapies or a lower cost alternative is desired.

Toceranib phosphate (Palladia) and masitinib (Kinavet) are orally administered TKIs that have efficacy against gross disease. While these drugs can be considered as adjuvant treatment, there is no data currently to define the efficacy of TKIs alone in the adjuvant setting. In the author’s practice, toceranib is discussed as an option for primary adjuvant therapy in cases when an owner declines intravenous treatment for their pet or subsequent to traditional chemotherapy when the presence of a c-kit mutation is known. In the treatment of bulky disease, Toceranib has a response rate of about 40% (~60% if stable disease is included). While dogs with KIT mutations were more likely to have a response than those without (69% vs. 37%), routine testing prior to toceranib therapy is probably not indicated for bulky disease as tumor response will guide therapy. Adverse effects include GI toxicity, mild to moderate leukopenia, and occasional muscle pain or mild PLN. Tolerability of toceranib improves when doses lower than the label dosage are used (2.5-2.75 mg/kg EOD or M,W,F). Combination of toceranib with vinblastine chemotherapy and palliative radiation therapy has also been studied.

Masitinib is conditionally approved for the treatment of nonresectable grade II or III cutaneous MCTs as a first-line therapy. Treatment with masitinib (12.5 mg/kg daily) has been shown to improve time to progression and survival rates at 12 and 24 months for dogs harboring activating c-kit mutations. Thus, this drug can provide the potential for long-term disease stabilization in some dogs. Adverse effects include mild GI toxicity, mild myelosuppression, occasionally PLN, and rarely hemolytic anemia. An appropriate monitoring schedule is important when treatment with oral TKIs is employed. When significant adverse effects are noted, treatment is typically discontinued for a period of time. In the author’s experience, it can often be restarted at a lower dose.

Ancillary therapy

Histamine blockers (H1 and H2) are indicated for cases when gross disease is present, either preoperatively or in the palliative setting for nonresectable masses/metastatic disease. Diphenhydramine (2 mg/kg BID-TID) and famotidine (0.5 mg/kg QD-BID) are common choices.

Clinical management of mast cell tumors can be challenging due to the wide range of biologic behavior. Although many cases are cured with adequate local therapy, the use of prognostic indicators discussed can help guide the clinician in determining which tumors are more likely to behave aggressively, and thus, become life-threatening for the dog. When clear poor prognostic factors exist, complete staging and adjuvant therapy is strongly advised. However, uncertainty regarding prognosis may remain in some cases despite our best efforts to define tumor behavior. This highlights the importance of owner education and clinical judgment in selecting appropriate diagnostic and therapeutic options.