Introduction:

Canine mast cell tumors (MCT) are by far the most common malignant skin tumor in the dog. There is tremendous variation in the clinical presentation, histologic appearance and biologic behavior. They range from histologically and biologically benign to histologically and biologically malignant. Fortunately, the majority of MCTs are limited to localized disease and can be cured with surgery alone. Recognizing the features that characterize high-risk patients and understanding the treatment options for both locoregional control and distant metastasis are crucial for adequate management of this disease. Recent advancements for local and systemic treatment of MCT has increased the therapeutic options available to veterinarians and owners.

Incidence and Risk Factors:

Mast cell tumors are the most common cutaneous tumor in the dog, accounting for 16% to 21% of cutaneous tumors. Most occur in mixed breeds, although Boxers, Rhodesian Ridgebacks, Pugs, Boston Terriers, Pitbull Terrier and Weimaraners are at higher risk (4 to 8 times more than the general population) for developing MCTs. Shar-Peis, particularly young dogs, are predisposed to developing poorly differentiated and biologically aggressive MCT. Conversely, Bostons and Pugs tend to develop multiple small, indolent MCT. The etiology of MCTs is largely unknown. Recently, expression of c-kit, a tyrosine kinase receptor, has been demonstrated in both canine and feline MCTs. Mutations in c-kit appear to be more common in high-grade MCTs and may be associated with a poorer prognosis.

Diagnosis:

Canine MCTs can look and feel like anything and they commonly mimic soft, subcutaneous masses that feel like lipomas. Fine-needle aspiration with cytology is a quick and easy test to help distinguish MCT from other tumors. Cytology is sufficient to achieve a diagnosis of MCT in approximately 90% of dogs. The classic appearance is a population of large round cells with central nuclei and abundant cytoplasm, with characteristic blue-purple cytoplasmic granules. Granules will not be visible in approximately 10% of MCT, which may make it difficult to obtain a definitive diagnosis in a small number of cases.

To Stage or Not To Stage:

The majority of canine MCT are unlikely to metastasize. However, there are some factors which help determine which MCT are likely to behave more aggressively.

1. **Location** – tumors in the preputial, perianal, oral, subungual (nail bed), and other mucocutaneous sites may have a worse prognosis as these tumors are more likely to metastasize.
2. **Recurrence** following initial surgical excision is a negative prognostic indicator as it may indicate a more aggressive or infiltrative growth pattern.

3. The presence of **systemic signs** (such as anorexia, vomiting, hematemesis, and melena) is a negative prognostic indicator because it often indicates systemic involvement.

4. Recent **rapid growth** and **tumor ulceration** are worrying signs that can indicate a high grade MCT.

Animals with MCTs displaying any of these criteria may have a higher likelihood of a high grade tumor and of metastasis. Knowing which tumors are more likely to behave aggressively helps identify those patients in which additional staging should be performed preoperatively, since this information may affect prognosis and alter the recommended treatment course, which may in turn influence a client’s treatment decision.

**Histologic grade** is one of the strongest prognostic factors. Since the 1980s, most veterinary pathologists have used the Patnaik system that divides canine cutaneous MCTs into 3 grades. Dogs with grade 3 tumors have a considerably worse prognosis than dogs with grade 1 tumors. However, dogs with grade 2 tumors can have a very variable outcome. Because of this, a 2-tiered system was recently developed to achieve better concordance between pathologists and more reliable prognostic information. This system divides MCTs into low-grade and high-grade tumors. A recent study found that the median survival times (MST) for low-grade MCTs was greater than 2 years, whereas it was less than 4 months for high-grade tumors. In both grading systems, the number of mitotic figures is an important parameter. Mitotic Index, or MI, is the number of mitotic figures seen in 10 high power fields. One study showed that regardless of histological grade, dogs with an MI < 5 have a MST of over 5 years, compared to less than one year for dogs with an MI > 5. The above grading systems to not apply to subcutaneous MCTs or MCT at other sites (such as oral mucosa). For subcutaneous MCT tumors, MI and histologic growth pattern (infiltrative vs. circumscribed) appear to be predictive for recurrence and overall survival.

**Clinical stage:** dogs with regional metastasis to draining lymph nodes may have a less favorable prognosis, and dogs with distant metastasis to the reticuloendothelial system (spleen, liver, and bone marrow) usually have a poor long-term prognosis.

**Additional factors:** other factors that may have a prognostic role include rate of tumor growth, size of tumor, poorly defined/diffuse tumors, and tumor ulceration.

A thorough search for metastasis (staging evaluation) prior to undertaking definitive therapy is recommended for any dog with one or more risk factors. Complete staging tests include CBC, chemistry profile, urinalysis, and cytological evaluation of the regional (draining) lymph node. Ultrasound can be used for inguinal and axillary lymph nodes. These lymph nodes are often not palpable even when enlarged, but can be easily found with ultrasound and an ultrasound-guided aspirate obtained if indicated. Abdominal ultrasound with aspirates of the liver and spleen is recommended for all dogs with metastasis to the regional lymph node. A recent publication suggested that the liver and spleen can have a normal ultrasonographic appearance even when metastatic MCT is present. In addition, ultrasound-guided aspirates should be obtained of any enlarged internal lymph nodes (such as the sublumbar and occasionally sternal lymph nodes). The utility of other tests such as bone marrow aspiration cytology and buffy coat smear is questionable at best and is not routinely performed at Penn Vet unless there are significant CBC abnormalities suggestive of bone marrow involvement.
Overview of treatment options:

If no evidence of regional or distant metastasis is found, local therapy should be pursued. Many MCT can be cured by surgical excision with appropriate surgical margins. For patients with inadequate surgical margins, radiation therapy can be very effective in preventing local recurrence, and is the treatment of choice in these cases. Inadequate margins includes most dogs with incomplete (“dirty”) margins and dogs with marginal (“clean but close”) margins that have risk factors including large or rapidly growing MCT, grade III tumors, and tumors with an infiltrative growth pattern. In addition, dogs with risk factors will typically receive prophylactic radiation to the draining lymph node.

For dogs with metastasis to the regional lymph node but no evidence of distant metastasis, the draining lymph node should be surgically removed along with the primary tumor. In addition, systemic therapy should be considered irrespective of histologic grade. A large percentage of dogs with lymph node metastasis can still be cured with multi-modality therapy.

For dogs with metastasis to lymph nodes beyond the first draining lymph node, or to distant sites including the liver and spleen, the role of surgery and radiation is less clear. Surgical removal when feasible, or radiation therapy when surgical removal is not an option, may help palliate symptoms associated with the primary tumor such as ulceration, bleeding, and pain. However, these treatments will not affect systemic progression of MCT.

When to offer surgery:

Surgery is the mainstay of treatment for the majority of canine MCT. In many cases, complete surgical excision is the only treatment needed to obtain a cure. In cases where a surgical cure is not obtained (either because of residual local disease or because of the risk of distant metastasis) the goal of surgery is to decrease the tumor burden as much as possible. Adjuvant therapies (radiation and chemotherapy) are much more likely to be effective when only minimal residual disease is present.

When planning a surgical approach, the goal is usually to obtain complete margins, including adequate lateral and deep margins. Fascia and collagen-dense tissues are good barriers to tumor infiltration. The deep margin should include a fascial plane deep to the tumor. Normal tissue margins should always be identified after removal so that the pathologist can assess the completeness of resection. In cases of incomplete resection, revision surgery is considered first when feasible. For low-grade tumors, narrow histologic margins of about 3 mm are probably adequate to prevent local tumor recurrence. It must be remembered that a surgical margin of about 2 cm is required to obtain an adequate histologic margin.

Recent post-surgical studies have indicated that recurrence in the face of microscopically incomplete margins is not absolute and may actually occur in only 50% of cases involving grade 1 or 2 tumors. However, clients should be counseled that the risks of “watchful waiting” include the chance that a recurrent tumor may be more biologically aggressive, metastatic spread may occur as the tumor regrows, and the recurrent tumor may be less amenable to a second surgical resection.

Conversely, for high-grade/Grade 3 tumors, about one third will recur despite ≥3 cm surgical margins and ≥of 3 mm histologic margins. For these tumors, adjuvant treatment should always be considered.
In cases where a surgical approach may not obtain complete margins, it is helpful for the surgeon to consult with a radiation oncologist prior to surgery to discuss postoperative radiation therapy. If this is not possible, detailed tumor measurements, photographs, and 3-dimensional imaging all facilitate subsequent radiation planning. For low-grade (Grade I and II) MCT, 2cm lateral margin appeared adequate.

If a surgical cure would require extensive surgery (such as flap grafts or limb amputation), the owner may opt for a more conservative marginal resection (with the knowledge that the surgical margins will not be complete) followed by radiation therapy as soon as the incision has healed. It is important to note that in this situation, the surgical approach must be able to reduce the tumor to microscopic disease. If visible tumor remains, there is an increased risk of wound complications and dehiscence (due to degranulation of the residual mast cells), and a decreased chance that post-operative radiation will be curative.

If a MCT is too large for a surgical approach at presentation chemotherapy can be attempted to shrink the tumor to a more manageable size. In select cases, radiation can also be used to shrink a tumor preoperatively, but this approach is rarely used.

**When to offer radiation therapy:**

Radiation therapy is most commonly employed to treat residual disease following incomplete surgical resection. Ideally radiation is started as soon as the surgical incision has healed. The draining lymph node will be treated prophylactically in most cases. If the draining lymph node was removed at the time of surgery, the lymph node bed will be treated if metastasis was present. Radiation is administered in small doses given 5 days a week (Monday through Friday) for about 3 ½ weeks. In this setting, radiation therapy prevents locoregional recurrence in 80-90% of patients.

For relatively small, low/intermediate grade MCT in which surgery is not an option (either due to owner preference or tumor location), radiation therapy may be curative, although the likelihood of cure is lower than when using radiation therapy postoperatively.

For large MCT, palliative radiation therapy can be used to shrink down the tumor and alleviate symptoms such as ulceration, bleeding, pain, and mechanical obstruction. Treatments consist of a few (2 to 6) large doses of radiation usually given once a week.

**Neoadjuvant therapy:**

Neoadjuvant therapy is the administration of therapeutic agents before the primary treatment in order to reduce the difficulty and morbidity of more extensive procedures. This can be considered for dogs with tumors that are large or located in technically challenging areas (such as the muzzle, distal limbs, and perineum) where adequate surgical margins cannot be achieved. Chemotherapy, such as prednisone alone or prednisone combined with cytotoxic drugs such as vinblastine, can be started as soon as staging tests have been completed. It is important hold off on chemotherapy (including prednisone) until staging tests are completed because these drugs can significantly alter test results. In most cases MCTs will shrink within 7 to 14 days. It is important to schedule surgery in a timely fashion, before tumor regrowth occurs. Occasionally an MCT can shrink to the point it is not detectable. To avoid this possibility it can be helpful to shave the fur in the area of the tumor and outline it with indelible ink before starting neoadjuvant therapy. When using vinblastine, a CBC should be checked prior to surgery to rule out significant
neutropenia. If present, a few days delay may be needed until the white blood cell count returns to a safe level for surgery.

**When to offer chemotherapy?**

Systemic chemotherapy should be considered for dogs with metastasis and dogs at risk for metastasis (according to the criteria listed above) and should be started as soon as the surgical site has healed. Systemic chemotherapy can also be considered for dogs at risk of local recurrence following surgery (according to the criteria listed above) and for which radiation therapy is not an option. For dogs in which aggressive surgery or radiation therapy are not feasible (either due to owner preference or medical constraints), chemotherapy can be given to dogs with gross disease, with or without metastasis.

There are numerous publications in the veterinary literature evaluating the response of gross MCT to conventional chemotherapy protocols. Response rates range from about 20% for prednisone alone to 65% for the combination of prednisone, vinblastine, and lomustine (CCNU). Response rates include dogs with both complete responses (no detectable tumors) and partial responses (significant decrease in tumor size). Duration of response is typically 2-5 months. When a dog progresses on a chemotherapy protocol, a protocol using different drugs can be tried.

There is much less published information on the use of adjuvant chemotherapy for high-risk MCT. The oncology group at Penn Vet currently uses a combination of vinblastine and prednisone. A study evaluating this protocol for dogs with high-risk MCT had a median survival time of almost 4 years. This study also suggested that prophylactic radiation of the draining lymph node may improve the disease-free interval and overall survival for these patients.

A new class of drugs called tyrosine kinase inhibitors (TKI) has been recently evaluated in canine MCT. These drugs work through a different mechanism of action than conventional cytotoxic drugs, by inhibiting cell surface receptors that are needed for cell division. Palladia (toceranib phosphate) is one of the few drugs specifically licensed for use in veterinary oncology. It is a tablet given every other day (or 3 days a week) as long as it is providing tumor control and is tolerated by the patient. The labeled indication for Palladia is “for the treatment of Patnaik grade II or III, recurrent, cutaneous mast cell tumors with or without regional lymph node involvement in dogs”. This drug has not been evaluated in the adjuvant setting (following the primary treatment of surgery and/or radiation therapy) as a treatment to delay or prevent recurrence and/or metastasis in high-risk dogs. Palladia has a risk of side effects, including serious side effects, which is comparable to other chemotherapy drugs used to treat MCT. The oncology group at Penn Vet uses Palladia in dogs that have gross disease that has progressed on conventional chemotherapy.

**When to start supportive medications?**

Rapid degranulation of neoplastic mast cells may occur spontaneously, or as a sequela following surgery, chemotherapy, or radiation. This release of histamine results in gastrointestinal ulceration. One study showed that a large percentage of asymptomatic dogs with MCT had evidence of subclinical gastrointestinal ulceration. Therefore, all dogs with measurable MCT or with mastocytosis should receive medication to mitigate gastric acid secretion triggered by histamine. Famotidine works through competitive inhibition of H₂ receptors on the gastric parietal cells. Omeprazole inhibits gastric acid
production through proton pump inhibition of gastric parietal cells, and recent evidence suggests it is more effective than \( H_2 \) inhibitors. Dogs with clinical evidence of bleeding due to gastrointestinal ulceration may benefit from the addition of sucralfate. Sucralfate reacts with stomach acid to form a viscous, adherent, substance that binds to the surface of both gastric and duodenal ulcers, preventing further damage from stomach acid and digestive enzymes and allows them to heal. \( H_1 \) antagonists such as diphenhydramine can help prevent both local and systemic allergic reactions such as wheal and flare (hives), pruritus, and anaphylactic symptoms (hypotension, tachycardia, nausea). This class of drugs may also minimize the negative effects of local histamine release on fibroplasia and wound healing.