Practical Approach to Management of Mast Cell Tumours in Dogs & Cats
67th Convention of the Canadian Veterinary Medical Association, 2015
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\textbf{Introduction}

Mast cell tumours (MCT) (histiocytic mastocytoma, mast cell sarcoma, mastocytosis) are the most common cutaneous tumour in the dog representing 20–25\% of all canine skin tumours. In the cat MCT represent 15\% of all tumours (second most common cutaneous tumour). No sex predilection has been found in the dog, but in the cat the male:female ratio is 2:1. MCT occur most commonly in middle-aged dogs and cats with a mean age of about 8 years. Siamese cats, boxers, Boston terriers, and other breeds of bulldog descendants are at higher risk to develop MCT.\textsuperscript{1,2}

Mast cell tumours may exist in cutaneous or extracutaneous sites. In dogs, the most common sites are the skin of the trunk and perineal region (50\%), the skin of the extremities (40\%), and the cutaneous head and neck (10\%). MCT can arise in multiple cutaneous locations (11\%). In cats, most MCT are found in the head and neck region. Occasionally, MCT are located only in the spleen in cats.\textsuperscript{1,2}

The biologic behaviour of MCTs is extremely variable. Histologic grading can help determine the likelihood of recurrence or metastasis, but it will not predict the biologic behaviour of an individual tumour. Mast cell tumours have a high metastatic potential and many dogs will present with regional lymph node metastasis or, rarely, splenic metastasis with splenomegaly. Dogs with advanced disease may have gastric or duodenal ulcers (related to histamine levels with secondary excess of hydrochloric acid secretion in the stomach) and present with vomiting, melena, and anemia. Occasionally, mechanical manipulation during examination will result in degranulation of mast cells, which results in erythema and wheal formation (Darier sign).\textsuperscript{1,2}

Diagnosis of MCT can often be made by a fine-needle aspirate (FNA) cytology, but excisional biopsy is required for accurate histologic grading. Establishing a diagnosis prior to surgical treatment can be very helpful because the treatment should be aggressive and precaution may need to be taken to prevent or control heparin and histamine release. Diagnostic workup may consist of staging with a complete blood count (CBC) (eosinophilia, basophilia, mast cells), buffy coat smear, bone marrow aspirate, FNA of the lesion and regional lymph node, abdominal radiographs or ultrasound (splenomegaly). In advanced canine MCT, a coagulogram (PT, PTT, FDP) may be performed.\textsuperscript{1,2} The presence of the occasional mast cell in buffy coat or draining lymph node must be interpreted with caution because non-neoplastic diseases can also result in mast cells.\textsuperscript{3} The tumour biopsy may be submitted for additional tests, such as immunohistochemistry (IHC) for markers of Ki67, c-kit mutations (CD117), and proliferation markers such as AgNOR staining and mitotic index.\textsuperscript{4,5}
**Staging**

After diagnosis of a MCT, it is important to consider the staging that will be necessary for each patient. In all cases, the draining lymph nodes should be palpated, when external and a FNA and cytology should be performed. If the draining lymph nodes are internal, an abdominal ultrasound may be necessary to examine the regional nodes. The decision whether or not to do an abdominal ultrasound for staging of MCT is clinician and case-dependent. In cases with large masses, recurrent disease, or lymph node involvement, an abdominal ultrasound should be performed. Small dermal MCT that are amenable to wide resection can be removed with a wide margin and then staging decisions can be made once the histological grade is available. If an abdominal ultrasound is performed, further controversy exists about whether or not to perform a FNA of the spleen and liver if they are ultrasonographically normal. There is literature that suggests that because metastasis of MCT tends to be infiltrative, rather than nodular, the spleen and liver should be aspirated in all cases. There is also literature that supports the view that only spleen and liver that are abnormal on ultrasound should be aspirated because when the spleen/liver are normal on ultrasound, the diagnosis of metastasis is rare. Although there is only a small number of studies evaluating the utility of thoracic radiographs for staging of MCT, the rate of detecting radiographic lung metastasis is low. Thoracic radiography may be warranted, however, as a method of ensuring that there is no concurrent disease in these patients or evaluating hilar lymph nodes. The evaluation of the buffy coat for mast cells is now considered historical only. Further, bone marrow aspiration is also not routinely done because dogs with bone marrow involvement will have widespread and severe disease before the bone marrow is affected.

**Therapy**

The therapeutic approach for MCT is based on the clinical stage and histologic grade of the tumour.

**Surgery**

Surgery is the primary treatment for MCT, particularly for control of local disease. In general, a wide resection is recommended for mast cell tumours. The exact margin required is not definitively known. A recent paper has suggested that 2-cm margins laterally are all that is required for tumours that are grade I or II. However, a subsequent study indicated that when 2-cm margins are used for grade II MCTs, 10% of the cases had dirty margins. Because of this, we recommend 3-cm lateral margins when possible and one fascial plane deep to the tumour. It has also been suggested that neoadjuvant treatment with corticosteroids may facilitate resection. Corticosteroids will decrease inflammation of the tumour and this may make resection easier; however, the corticosteroids will not have an effect on the tumour cells that are peripheral to the tumour. It is possible that corticosteroid treatment may create a false sense of security and the ability to achieve clean margins. It is the author’s opinion that corticosteroid use preoperatively should be reserved for cases where cytoreductive surgery and a marginal resection are the goals of surgical therapy.

**Radiotherapy**

Radiotherapy has played an important role in the management and treatment of canine cutaneous MCT. As with most tumour types, radiation therapy is used for the purpose of achieving local and regional control of the tumour. If excision of a cutaneous mast cell tumour is incomplete, a second and wider surgery should be
considered. If, due to the location and/or size of the scar, re-excision is not possible, radiotherapy is the treatment of choice. Curative-intent radiation schedules of daily small-dose fractions for 3 to 4 weeks (total dose approximately 40–52 Gray) have proven to be effective for local control of incompletely excised cutaneous MCT.\textsuperscript{1} Two-year control rates of 85–95% are reported when low- or intermediate-grade MCT are treated in this manner.\textsuperscript{7} It is important to note that the reported recurrence rate of incompletely excised grade II MCT is approximately 23%, suggesting that a minority of incompletely excised MCT recur and that adjuvant therapies may not always be necessary.\textsuperscript{8a} However, local recurrence has been shown to negatively affect the survival of affected dogs,\textsuperscript{8a} and adjuvant radiotherapy remains the treatment of choice to minimize the risk of local recurrence if complete surgical excision is not possible. When regional lymph node metastasis is present, extirpation of the affected node is recommended along with excision of the primary tumour. It has been reported that dogs with low-to-intermediate grade MCT with metastasis limited to the local regional lymph node may have a favourable prognosis (median disease free interval of 41 months) when treated with a combination of surgery and definitive (curative-intent) radiation therapy.\textsuperscript{8b} These findings suggest that systemic therapy may not be necessary for some dogs with low- and intermediate-grade tumours that might intuitively be considered “high risk,” such as those with lymph node metastasis. Additional studies are needed to confirm this conclusion. In the meantime, adjuvant systemic therapy should be considered in dogs with negative prognostic factors including high-grade tumours, lymph node metastasis, recurrent tumours, tumour ulceration, GI signs, tumours in unfavourable locations, rapid tumour growth, and large tumours.\textsuperscript{1} For incompletely excised grade III or high-grade MCT, numerous radiotherapy schedules have been proposed, including standardly fractionated (daily, small-dose fractions for 3 to 4 weeks) and coarse-fractioned protocols (weekly, large-dose fractions for 3 to 4 weeks), but these have not been compared.\textsuperscript{1} Systemic adjuvant therapy is recommended for grade III or high-grade MCT due to the higher metastatic potential. Interestingly, a report described positive outcomes in dogs with grade III MCT treated with surgery and radiation alone, including the regional lymph node (median remission and survival times of 28 months).\textsuperscript{8c} Despite these interesting findings, the majority of veterinary oncologists feel that local therapy alone is insufficient for optimal control of poorly differentiated or high-grade MCT.

Radiation therapy can also serve as a means to achieve palliation of clinical signs associated with non-resectable tumours. Although irradiation of bulky MCTs is generally less effective than treatment of microscopic disease, excellent tumour responses may be observed, including complete responses. Coarse-fraction protocols (weekly, large-dose fractions for 3 to 4 weeks) are commonly used for palliation. Tumour response rates greater than 70–80% have been reported when MCTs were irradiated in the gross disease setting in combination with Palladia\textsuperscript{33} and/or glucocorticosteroids\textsuperscript{8d,8e}. Degranulation of tumours in response to irradiation is possible, but rare. This may be of more concern when large tumours are treated. Ancillary medications such as those suggested below and glucocorticoids should be used when MCTs are irradiated in the gross disease setting.

Radiation therapy has reported a 50–75% control rate at one year. When possible, radiation should be used as adjuvant therapy after incomplete surgical excision or as primary treatment if surgery is not an option.\textsuperscript{9–12}
Chemotherapy

Chemotherapy is less effective than surgery or radiation. However, multiple tumours or advanced local disease can only be managed by chemotherapy and although remissions may be achieved, cure is unlikely. In dogs, glucocorticoid therapy (oral prednisone [0.5–1.0 mg/kg PO or 20–40 mg/m² PO q 24 h] or triamcinolone [1 mg/cm diameter of tumour intralesionally q 2 weeks]) frequently results in partial remission (PR) or occasionally complete remission (CR); however, feline MCT appears to be less responsive to glucocorticoids. Remission times are usually 10–20 weeks; however, dogs that are tumour free after 6 months have a low incidence of recurrence and therefore therapy is usually discontinued at that time. Multiagent protocols (e.g., prednisone and vinblastine) may achieve a higher response rate than single agent therapy.1,2,13 Recently, tyrosine kinase inhibitors (TKI) (toceranib [Palladia], masitinib [Kinovet], imatinib [Gleevec]) have become more available in veterinary medicine.14-21 Kit, a tyrosine kinase, has been found to be mutated in 9–30% of high-grade MCT in dogs.15 In future, TKIs in combination with other chemotherapy may result in higher response rates.

Ancillary Drug Therapy

Ancillary drug therapy is important with canine MCT. Dogs with mastocytosis, palpable MCT, or evidence of gastrointestinal bleeding should receive H₂ antagonists (i.e., famotidine, ranitidine) to reduce gastric acid secretion and prevent gastrointestinal ulceration. Sucralfate (0.5–1 g PO q 8h) may be given in cases with evidence of gastrointestinal ulceration and bleeding. H₁ antagonists (e.g., diphenhydramine 2–4 mg/kg PO q 12 h) are used along with famotidine prior to and following surgical removal of canine MCT to help prevent the negative effects of local histamine release on fibroplasia wound healing.1,2

Prognosis

Prognosis is based on species, breed, tumour location, growth rate, extent of disease, and the histologic grading of the tumours. The grading is based upon cellular differentiation, cellular pleomorphism, cytoplasmic granules, mitotic figures, and depth of invasion. In general, cutaneous MCT carry a more guarded prognosis in the dog than in the cat. MCT in the boxer are usually of a lower histologic grade than those found in other breeds. MCT in Siamese are of the less malignant histiocytic type. Tumours located in the perineal or preputial area are likely to metastasize both locally and to deep lymph nodes. Growth rate, but not tumour size, is also an important prognostic indicator. Dogs with MCT growth rates of greater than 1 cm/week have only a 25% chance of surviving an additional 30 weeks. The more undifferentiated tumour then the higher the grade and the poorer the prognosis.1,2,22

Regardless of local therapy chosen, even dogs with low-to-intermediate grade tumours should be evaluated regularly for local recurrence and possible systemic spread.

Chemotherapeutic Protocols for Canine Mast Cell Tumour23

Prednisone/Vinblastine29

Prednisone 2 mg/kg PO q 24 h; vinblastine 2 mg/m² IV q weekly for 4 weeks followed by 4 treatments every 2 weeks.
Continue vinblastine 2 mg/m\(^2\) IV every 2 weeks for as long as appears to have an objective response. Taper and discontinue prednisone over 12–26 weeks.

**Tyrosine Kinase Inhibitors (TKI)**

- **Toceranib** (Palladia)\(^ {14-16} \)
  - (3.25 mg/kg PO q 48 h)
  - 2.5–2.7 mg/kg MWF
- **Masitinib** (Kinave)(17)
  - 12.5 mg/kg PO q 24 h
- **Imatinib** (Gleevec)\(^ {18,21} \)
  - 5 to 10 mg/kg PO q 24 h

**CCNU (Lomustine)\(^ {28} \)**

- CCNU (lomustine) 70–90 mg/m\(^2\) PO every 3 weeks

**Prednisone\(^ {24,25} \)**

- Prednisone 1 mg/kg PO q 24 h
  - or
  - Prednisone 40 mg/m\(^2\) PO q 24 h for 1 week, then 20 mg/m\(^2\) PO q 24 h for 3 weeks, then 20 mg/m\(^2\) PO q 48 h for 3 weeks,
  - Then reduce dose by 50% every 3 weeks to lowest dose that maintains remission or stable disease.

**Triamcinolone\(^ {26,27} \)**

- Triamcinolone 3–6 mg/dog intralesionally once/week
  - or
  - Triamcinolone 1 mg/cm tumour diameter, maximal dose 10–40 mg, q 14 days

**CVP\(^ {30,31} \)**

- (Cyclophosphamide/Vinblastine/Prednisone)
  - Cyclophosphamide 50 mg/m\(^2\) PO q 48 h or for 4 days per week; Vinblastine 2 mg/m\(^2\) IV once a week; Prednisone 20–40 mg/m\(^2\) PO q 48 h
  - or
  - Day 1 vinblastine 2–3 mg/m\(^2\) IV (start at 2 mg/m\(^2\) and increase by 10–30% with each dose if tolerated); Days 8,9,10,11 cyclophosphamide 50–75 mg/m\(^2\) PO ; Daily prednisone 1 mg/kg PO q 24 h
  - Repeat cycle at Day 21 for 6 months. Prednisone tapering began at 4 months and discontinued by 7 months.

**References**
VIN editor: References 8d and 11 are the same; references 24 and 29 are the same. There are two references 23.


**Speaker Information**
(click the speaker's name to view other papers and abstracts submitted by this speaker)

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