INTRODUCTION
Mast cell tumour (MCT) represents the most common malignant cutaneous tumour in the dog, and the second most common cutaneous tumour in the cat. There is a large degree of variation in the histologic appearance and biologic behaviour of MCT, ranging from histologically and behaviourally benign to histologically and behaviourally malignant. However, 65 to 80% of MCT will remain local diseases. Knowledge of the signs associated with worrisome prognosis, and the steps to take to address the potential for recurrence and/or metastasis, can help to simplify the approach to this sometimes frustrating neoplasm. Likewise, newer information regarding local and systemic treatment of MCT has increased the management options available for veterinarians and owners to consider.

CANINE MCT
PREVALENCE AND RISK FACTORS
Mast cell tumours (MCT) represent the most common cutaneous tumour in the dog, accounting for between 16 and 21% of all cutaneous tumours. MCT are primarily a disease of older dogs with a mean age of 9 years. Most occur in mixed breeds; however, boxers, Boston terriers, Labrador retrievers, beagles, and schnauzers have all been reported to be predisposed. While boxers and other brachycephalic breeds may be at increased risk for MCT development, they more commonly develop histologically low or intermediate grade forms of the disease, which carry a more favorable prognosis. Anecdotally, Shar Peis have been reported to have a tendency to develop aggressive MCT. No sex predilection has been reported.

The aetiology of MCT in the dog is for the most part unknown. Evidence is lacking for a viral aetiology, and no contributing environmental factors have been identified.

DIAGNOSIS
Canine MCT have been referred to as “the great pretender”, because they can look and feel like anything. This can include soft, subcutaneous masses that can feel exactly like lipomas. Thus, needle aspiration cytology should be offered for any lump or bump encountered. 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 confound the diagnosis in a small number of cases. It is common to see other inflammatory cells, such as eosinophils and neutrophils, admixed with the MCT cells.

When a presumptive diagnosis of MCT is made, it is useful to perform needle aspiration cytology of the regional lymph node at the same time, whether or not it feels enlarged, to rule out early metastasis.

TO STAGE OR NOT TO STAGE
The majority of canine MCT, while locally aggressive, are unlikely to metastasize. Having an idea of which are likely to behave aggressively prior to surgery may help to identify those patients in which additional staging, to rule out disease elsewhere, should be undertaken preoperatively.

Prior studies have identified several prognostic factors associated with MCT: (1) Histologic grade is one of the strongest -- dogs with high-grade (grade III) tumours may die of their disease rapidly.
despite appropriate local therapy; however, this information is not available until after resection unless incisional biopsy is performed; (2) Clinical stage - Dogs with metastasis to regional lymph nodes or other structures at presentation have a less favorable long-term prognosis; (3) Location - Tumours in the preputial, perianal, oral, subungual (nail bed) and other mucocutaneous sites classically have worse prognoses; (4) Recurrence following initial surgical excision is a negative prognostic indicator; (5) The presence of systemic signs (anorexia, vomiting, hematemesis, melena) is a strong negative prognostic indicator, as it often indicates systemic dissemination; (6) Recent rapid growth or tumour ulceration are also worrying signs.

Animals with tumours displaying these criteria may have a higher likelihood of metastasis, and thus a thorough search for disease elsewhere is reasonable prior to undertaking definitive therapy. This may also be reasonable in lower-risk patients if very expensive or aggressive treatment is likely to be necessary, or if the tumour is in a location not amenable to wide surgical excision. In the absence of these factors, it is reasonable to proceed immediately to appropriately aggressive surgical excision (See below).

Complete staging for canine MCT should include cytologic evaluation of the regional lymph node, abdominal ultrasound, and thoracic radiographs. Of these tests, abdominal ultrasound and lymph node cytology are the most likely to yield important results. Cytology of sonographically abnormal lymph nodes or organs in the abdomen is indicated, however aspirates of structurally normal liver and spleen can be challenging to interpret, as these organs can contain normal resident mast cells. If radical, expensive or potentially disfiguring surgery is being contemplated, an incisional biopsy may also be considered for histologic grading, if it will change the surgical approach or the owners’ willingness to pursue therapy. The utility of other tests such as bone marrow aspiration cytology and buffy coat smear is questionable at best.

If no evidence of disease elsewhere is found, appropriate local therapy can be pursued. Identification of disease in the regional lymph node means that this should be removed as well at the time of surgery, and that additional systemic therapy should be considered irrespective of histologic grade. Identification of disease beyond the regional lymph node usually means that surgery will be of little or no benefit.

Surgery for mast cell tumours

Even well-differentiated MCT are associated with aggressive local tissue infiltration. Thus, it is necessary to include a generous margin of normal-appearing tissue on all sides of the tumour (including deep) to ensure that any microscopic nests of tumour are removed. The standard recommendation is to remove a minimum of 3 cm of normal-appearing tissue 360 degrees around the tumour, and at least one normal fascial plane deep. The entire specimen should be submitted in one piece, preferably with the margins inked, so that the pathologist can assess all margins for adequacy of excision. There is accumulating information, however, that surgical margins less than 3 cm may be sufficient in “tight spots”. This seems especially true for low/intermediate grade tumours, and those that are fairly small in diameter.

When necessary, very aggressive or radical surgical procedures, such as amputation or body wall resection, are reasonable to consider. Prior to contemplating procedures such as these, complete staging is recommended, and incisional biopsy for determination of histologic grade may be helpful if it will alter the owner’s willingness to proceed. When dealing with a low or intermediate-grade tumour, very aggressive surgery is reasonable because the likelihood of metastasis is low.

The question of whether or not to administer perioperative histamine blockers is a matter of personal choice. The risk of a serious degranulation reaction is very small unless the tumour is extensively handled (which should not happen if 3 cm of normal tissue is removed!).
INTERPRETING THE PATHOLOGY REPORT

Three equally important pieces of information need to be gleaned from the pathology report: (1) Histologic grade; (2) Adequacy of surgical margins, and; (3) Mitotic index. If only a representative piece of the tumour is submitted, margins cannot be evaluated and the utility of the report is reduced. Pathologists often utilize a numeric grading scheme, where “Grade I” is well-differentiated and “Grade III” is poorly differentiated, however some pathologists will now utilize words such as “low, intermediate or high-grade” or “well, poorly or intermediately differentiated” in place of a numerical scale. If information regarding grade, margins or mitotic index is not provided, it should be requested from the pathologist.

Low or intermediate grade MCT with complete surgical margins usually require no further therapy, as the risk of recurrence or metastasis is only approximately 10%. However, regular rechecks for recurrence, metastasis, or new cutaneous masses is indicated. Low or intermediate grade tumours with incomplete surgical margins have a high chance of recurrence, but a low chance for metastasis. Thus, further aggressive local therapy is reasonable. When possible, immediate re-excision of the surgical scar (and an additional 3 cm tissue in all directions and another fascial plane deep) is the most useful treatment. The entire excised tissue should be inked and re-submitted for histopathology. When this is not possible, the next best option would be the use of radiation therapy. Chemotherapy may be useful to delay or prevent recurrence in cases where additional surgery or radiation therapy is not possible or has been declined.

High grade MCT with complete surgical margins have a low chance for recurrence, but a high chance for eventual metastasis. Systemic therapy (e.g. chemotherapy) can be offered in an attempt to delay or prevent this. High grade MCT with incomplete margins have a high likelihood of both recurrence and metastasis: Therapy designed to address both of these possibilities (e.g. additional surgery or radiotherapy, with chemotherapy) is optimal.

There is new information from 2 separate studies that assessment of mitotic index (a measure of the rate of proliferation, which can be assessed on any histology slide) may be a strong predictor of outcome, identifying intermediate grade tumours at higher risk of metastasis. The most commonly utilized mitotic index cutoff for distinguishing between “high-risk” and “low-risk” canine MCT is 5 mitoses per 10 high-powered fields: in one study, dogs undergoing surgery for MCT with less than 5 mitoses/hpf had a median survival time of 70 months, whereas those with more than 5 mitoses/hpf had a median survival time of 2 months.

SPECIAL STAINS AND GENETIC TESTS

A variety of specialized histochemical or immunohistochemical tests for assessment of proliferation (agyrophilic nucleolar organizer region, or AgNOR staining, Ki67, and proliferating cell nuclear antigen, or PCNA) have been evaluated for their predictive value and have likewise been demonstrated to correlate well with postsurgical outcome. However, it is not clear as yet whether these more cumbersome assessments provide any more prognostic information than that provided by simple assessment of mitotic index.

Recently, expression of KIT, a tyrosine kinase receptor for the hematopoietic growth factor stem cell factor (SCF), has been demonstrated in canine and feline MCT. Several studies have demonstrated, in 20-40% of canine MCT, the presence of mutations in the c-kit gene, leading to constitutive activation in the absence of bound SCF. Multiple investigators have evaluated the prognostic significance of the presence of c-kit gene mutations or alterations in the subcellular localization of the KIT protein, in canine MCT. In the majority of these studies, MCT possessing c-kit gene mutations or altered subcellular localization as assessed by immunohistochemistry (e.g. a shift from the normal membranous location to an intracellular location) are associated with an inferior prognosis when
compared to those with wild-type c-kit and normal KIT protein localization. Both c-kit gene sequencing and KIT protein immunohistochemistry are available through multiple academic laboratories in the U.S. KIT protein immunohistochemistry is available in the UK; however, c-kit gene sequencing is not available as yet.

CAUTION OWNERS AGAINST A “WAIT AND SEE” APPROACH
The importance of addressing the potential for local recurrence the very first time the tumour appears cannot be overstated. Owners should be strongly cautioned against adopting a “wait and see” attitude, with the intent of becoming more aggressive if/when the tumour grows back. Recurrent tumours are likely to grow more quickly, invade more deeply, and are more likely to ulcerate or become painful. In a recent study, dogs with MCT that were locally recurrent at the time systemic therapy was started were more than 4 times more likely to die as a result of MCT than dogs that started appropriate therapy at the first occurrence.

RADIATION THERAPY
Radiation therapy (RT) has proven to be a very effective local treatment modality when combined with “marginal” surgical excision for canine MCT. The majority of “curative intent” or “full-course” RT protocols in common use involve a series of 10 to 25 treatments delivered either Monday through Friday or three days per week for several weeks. 2-year control rates of 85 to 90% can be expected when incompletely excised low- or intermediate-grade MCT are treated with such RT protocols. “Coarsely fractionated” or “palliative” protocols, e.g. once-weekly RT, is also utilized for MCT; however, limited information exists regarding their efficacy. Radiation therapy to bulky tumours is consistently less effective than RT to microscopic disease, with one-year control rates of approximately 50%.

Animals receiving RT can develop varying degrees of a “sunburn-like” reaction at the site where the radiation is delivered. These can range from mild erythema and pruritus to moist, oozing or ulcerated skin. Many animals will need to wear an Elizabethan collar to prevent self-trauma and/or receive oral antibiotics or analgesics during this period. These effects typically do not start until the second or third week of treatment and are resolved within 2-4 weeks after the completion of RT. The animal can be left with an area of irradiated skin that is permanently hairless, the hair may grow back only partially, and may turn white within the radiation field. Chronic, long-term side effects are rare, but are more likely to occur with “palliative” protocols consisting of large weekly fractions.

CHEMOTHERAPY
Animals with undifferentiated MCT, MCT that have metastasized, or tumours in a historically unfavorable location (see above) may benefit from the addition of some form of systemic therapy to appropriate local therapy to attempt to delay or prevent metastasis. In addition, aggressive surgery or RT may be cosmetically unappealing or financially impossible for some owners. Similarly, dogs with multifocal or metastatic disease may not be candidates for surgical treatment. Multiple studies have been published investigating various systemic therapies for measurable canine MCT, the results of which are summarized in Table 1.
Table 1. Response to Medical Therapy in Measurable Canine Mast Cell Tumours

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Number Treated</th>
<th>%CR a</th>
<th>%PR b</th>
<th>%ORR c</th>
<th>Median Resp. Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>25</td>
<td>4%</td>
<td>16%</td>
<td>20%</td>
<td>NR d</td>
</tr>
<tr>
<td>Vincristine</td>
<td>27</td>
<td>0%</td>
<td>7%</td>
<td>7%</td>
<td>NR</td>
</tr>
<tr>
<td>CCNU (Lomustine)</td>
<td>21</td>
<td>6%</td>
<td>38%</td>
<td>44%</td>
<td>79 d e</td>
</tr>
<tr>
<td>Pred/Vinblastine</td>
<td>17</td>
<td>33%</td>
<td>13%</td>
<td>47%</td>
<td>154 d</td>
</tr>
<tr>
<td>P/C/V</td>
<td>11</td>
<td>18%</td>
<td>45%</td>
<td>63%</td>
<td>74 d</td>
</tr>
<tr>
<td>COP-HU g</td>
<td>17</td>
<td>23%</td>
<td>35%</td>
<td>59%</td>
<td>53 d</td>
</tr>
<tr>
<td>Pred/VBL/CCNU</td>
<td>37</td>
<td>24%</td>
<td>32%</td>
<td>57%</td>
<td>52 wks</td>
</tr>
<tr>
<td>LDI-100</td>
<td>17</td>
<td>29%</td>
<td>35%</td>
<td>64%</td>
<td>141 d / 66 d (CR/PR)</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>10</td>
<td>10%</td>
<td>30%</td>
<td>40%</td>
<td>74-90 d</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>46</td>
<td>4%</td>
<td>24%</td>
<td>28%</td>
<td>46 d (for PRs)</td>
</tr>
<tr>
<td>Pred/Chlorambucil</td>
<td>21</td>
<td>14%</td>
<td>24%</td>
<td>38%</td>
<td>533 d</td>
</tr>
</tbody>
</table>

a CR = Complete response  
b PR = Partial response  
c ORR = Overall response rate  
d NR = Not reported  
e Excludes patient that experienced a CR, euthanized without evidence of disease after 440 days  
f P/C/V = prednisone/cyclophosphamide/vinblastine  
g COP-HU = cyclophosphamide/vincristine/prednisone/hydroxyurea

Systematic evaluation of postoperative treatment for MCT at high risk of metastasis remains understudied. Historically, this “high-risk” designation includes high-grade/anaplastic MCT, MCT arising from mucous membranes, and MCT with regional metastasis. Recent evidence suggests that MCT with high indices of proliferation, as assessed via immunohistochemical means or assessment of mitotic index, may be candidates for postoperative chemotherapy as well, irrespective of grade.

Three studies have been published evaluating the efficacy of chemotherapy with prednisone and vinblastine (VBL) in the prevention of recurrence or metastasis in the post-surgical setting.

Prednisone and VBL administration - Prednisone is administered orally at an initial dose of 2 mg/kg daily, for the first week, and this dose is tapered and discontinued over approximately 3 months. VBL is given as a rapid intravenous bolus at 2 mg/m² every 1-2 weeks. The standard postoperative protocol consists of weekly injections for 4 weeks, followed by 4 biweekly injections.

Adverse Effects - Adverse effects are noted in approximately 20% of patients, usually after the first dose of VBL. These are mild in most. Mild adverse effects include self-limiting vomiting, neutropenia without evidence of sepsis (7-day neutrophil count less than 1,000/µL), or lethargy/soft stool. Severe adverse effects occur in only approximately 5% of patients.

Efficacy - Although randomized, placebo-controlled clinical trials are lacking, there is accumulating evidence from single-arm studies that adjuvant therapy for MCT at high risk for metastasis can improve patient outcome. In one study, 27 dogs with incompletely or marginally resected MCT, mostly of intermediate grade, were treated with prednisolone and VBL chemotherapy. Only one dog (3.7%) experienced local recurrence, and four (15%) developed another cutaneous MCT. A second study evaluated the use of postoperative prednisone and VBL for dogs with MCT considered to be at high risk for metastasis (node-positive, mucous membrane origin, or high histologic grade). In this study, dogs with high grade MCT had a median survival time of 1374 days. A third study reported 70% 1- and 2-year disease-free survival percentages following prednisone/VBL in high-grade MCT.
Interestingly, one study suggested a profound difference between the outcome of a high-grade tumour and an intermediate-grade tumour with lymph node metastasis. Despite the presence of lymph node metastasis, 90% of patients with grade II tumours with positive lymph nodes were disease-free at one year. Patients with grade III tumours treated in the adjuvant setting had 2-year survival rates of 60%. This appears to be a significant improvement over historical data employing surgery alone, which report a median survival of 8 months and a 2-year survival percentage of less than 15%.

There is information suggesting that many dogs may tolerate doses of VBL in excess of 2 mg/m². It remains to be seen if dose-escalation of VBL will translate into improved efficacy. Several investigators have reported on the efficacy of postoperative therapy with other drugs e.g. prednisone/lomustine, VBL/cyclophosphamide/prednisone, or VBL/lomustine/prednisone for postoperative MCT therapy, also with encouraging results.

Lomustine and prednisone was used to treat 10 dogs with incompletely resected grade II MCT. No dogs developed recurrence or regional / distant metastases, with 1 and 2 year progression free rates in surviving dogs of 100 and 77% respectively. However, 2 dogs died of liver toxicity. Typically, lomustine is dosed at around 70 mg/m² every 21 days. A serum biochemistry profile should be checked prior to each dose. If the ALT reaches >4x the top of normal range, treatment should be stopped. If the ALT starts to rise, liver protective agents such as SAMe/silymarin should be considered. Myelosuppression can be marked with lomustine (particularly neutropenia) and a CBC is recommended 7 days after the first dose and prior to subsequent doses. Nephrotoxicity is reported rarely with lomustine.

A combination of lomustine and VBL has been used both in the macroscopic disease setting and for residual microscopic disease. Fifty-six dogs were treated, 37 with macroscopic disease and 20 with microscopic disease (the latter were aggressive grade IIs or III). Lomustine was administered at approximately 50-60 mg/m² alternating with VBL at 2 mg/m². Dogs with microscopic disease had a median progression free survival time of 35 weeks and an overall survival of 48 weeks.

The combination therapy using cyclophosphamide, VBL and prednisone also showed promising results for both dogs with gross disease and in the microscopic residual disease setting / dogs considered at high risk of recurrence. For animals with microscopic disease, the PFST was 865 d and >2092 d, (however it should be noted that this patient group is not comparable with the lomustine VBL study above, since in the CVP study, 63% of dogs in group 2 either had clean margins or received RT).

This protocol consisted of:
Vinblastine IV q 3 weeks on day 1 of the protocol
Cyclophosphamide 200-250 mg/m² q 3 weeks either orally divided over days 8-11 or IV on day 8 (furosemide was administered at 2.2 mg/kg if given IV)
Prednisolone 1 mg/kg daily, gradually tapering over several weeks.

ANCILLARY THERAPY
Although these measures have no direct effect on tumour growth, ancillary therapy for the systemic effects of MCT related to degranulation is sometimes recommended. Mast cell tumour associated local swelling, erythema and pruritus is primarily mediated through histamine H₁ receptors, while histamine-induced gastrointestinal ulceration is primarily mediated through H₂ receptors. Blocking the histamine’s effects of release can be accomplished by administering the H₁ blockers diphenhydramine (2 - 4 mg/kg PO or IM q 8-12 hours) or chlorphenamine PO or IM and the H₂ blockers cimetidine (4-5.5 mg/kg PO or IV q 6-8 hours), famotidine (0.5-1 mg/kg PO, SQ or IV q 12 hours) or ranitidine (2
mg/kg PO, SQ or IV q 8-12 hours). Omeprazole (0.5-1 mg/kg PO q 24 hours), a proton pump inhibitor, is equally effective in MCT, although it may take several days to maximally inhibit gastric acid production.

The use of these agents is generally reserved for those cases where: (1) Systemic signs of illness are present; (2) The tumour is likely to be incised or extensively manipulated at surgery (i.e. cytoreductive surgery); (3) Treatment is undertaken where gross disease will remain and tumour degranulation is likely to occur in situ (e.g. RT or chemotherapy for tumours that are not cytoreduced). These agents are not routinely used for cases where wide surgical excision is to occur without excessive manipulation of the tumour itself. For cases with active evidence of gastrointestinal ulceration, the addition of sucralfate (0.5 to 1.0 g PO q 6-8 hours) and occasionally misoprostol (2-4 ug/kg PO q 8 hours) to histamine blockers is prudent.

Some experimental data suggest that the use of H1 and H2 blockers could also be beneficial for the prevention or resolution of histamine-mediated wound breakdown, but this has not been systematically evaluated. The use of protamine sulfate, a heparin antagonist, has been mentioned anecdotally for use in cases of severe intraoperative or therapy-induced hemorrhage.

RECEPTOR TYROSINE KINASE INHIBITORS

Introduction
Cancer is a disease characterized by dysregulated growth, abridged cell death, and enhanced cell migration, invasion and angiogenesis. While the molecular mechanisms responsible for conferring this phenotype are very diverse, one of the classes of molecule that has been receiving a great deal of recent attention as a potential target for therapy are the receptor tyrosine kinases (RTKs). These are cellular receptors for extracellular growth factors that facilitate communication from the extracellular milieu to the cell interior, mediating functions such as growth, survival, invasion and angiogenesis. A panoply of different RTKs are expressed by almost all tumour cells, but they can play variable roles in the pathogenesis of the disease.

Most RTKs exist as monomers, which homodimerize or heterodimerize upon contact with the appropriate ligand, inducing a conformational shift that allows phosphorylation of tyrosine residues in the intracellular domain. This then triggers several different intracellular second messenger cascades, culminating in altered gene expression and, often, a more malignant phenotype (Fig. 1).

![Diagram](https://via.placeholder.com/150)

**Figure 1.** Diagram of a generic receptor tyrosine kinase
There are several new cancer drugs currently available on the human market that act by inhibiting signaling through one or more RTKs, and many more are in late-stage clinical development (see below). In addition to their potential for off-label use in veterinary cancer patients, RTK inhibitors specifically labeled for use in veterinary patients are now available. Thus, an understanding of this class of protein and the drugs designed to inhibit RTK signaling will be critical as veterinary oncology advances in the next decade.

RTK Activation
Under most normal circumstances, activation of RTKs occurs only when the receptor encounters the appropriate ligand in the extracellular milieu. However, there are a variety of mechanisms by which RTKs can be inappropriately activated. These include: (1) Production of the ligand by the tumour cells themselves (autocrine stimulation); (2) Overexpression of the RTK, leading to spontaneous dimerization; (3) Mutations in the RTK, leading to constitutive activation in the absence of bound ligand. Any of these alterations can result in inappropriate signaling through the receptor, leading to an enhanced oncogenic phenotype.

RTK Inhibition And Human Cancer
One of the first tyrosine kinases to be definitively implicated in human tumourigenesis and successfully inhibited was the **bcr-abl** fusion protein (the product of the so-called Philadelphia chromosome translocation), demonstrated to be present and functional in many cases of chronic myelogenous leukemia (CML). This chimeric protein fuses the activation domain of the Bcr protein to the kinase domain of the Abl protein, rendering it constitutively active and capable of signaling at all times, providing an unending stimulus for cell proliferation and protection against cell death (apoptosis). Given the dependence on this fusion kinase for proliferation and survival in CML cells, an effort was made to find a drug capable of specifically inhibiting this signaling. This culminated in the discovery of a small molecule called STI571 (also called imatinib mesylate or Gleevec®). This molecule was capable of potently inhibiting signaling through the Abl kinase, resulting in diminished CML cell proliferation and enhanced cell death. This molecule showed excellent antitumour activity and a good safety profile in humans with CML, and is currently approved for that indication.

Since the successful approval of imatinib, many additional RTK inhibitors have been approved for use in human cancer (Table 2).

**Table 2. RTK Inhibitors Approved for Human Use**

<table>
<thead>
<tr>
<th>Name</th>
<th>Class</th>
<th>Targets</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Small molecule</td>
<td>Bcr-Abl, Kit, PDGFR</td>
<td>Chronic myelogenous leukemia (CML), gastrointestinal stromal tumour (GIST)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Monoclonal antibody</td>
<td>HER2 (erb2)</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Small molecules</td>
<td>EGFR</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Monoclonal antibody</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Monoclonal antibody</td>
<td>VEGFR2</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Small molecule</td>
<td>Kit, FLT3, VEGFR2/3, PDGFR</td>
<td>Renal cell carcinoma (RCC)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Small molecule</td>
<td>Kit, FLT3, VEGFR1-3, PDGFR, CSF-1R, RET</td>
<td>RCC, GIST</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Small molecule</td>
<td>Bcr-Abl, Src, KIT, EPHA2, PDGFR</td>
<td>CML, ALL</td>
</tr>
<tr>
<td><strong>Nilotinib (Tasigna®)</strong></td>
<td>Small molecule</td>
<td>Bcr-Abl, Kit, PDGFR</td>
<td>CML</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Lapatinib (Tykerb®)</strong></td>
<td>Small molecule</td>
<td>EGFR, HER2</td>
<td>Breast cancer</td>
</tr>
<tr>
<td><strong>Pantitumumab (Vectibix®)</strong></td>
<td>Monoclonal antibody</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td><strong>Pazopanib (Votrient®)</strong></td>
<td>Small molecule</td>
<td>VEGFR1-3, PDGFR, KIT</td>
<td>Renal cell carcinoma</td>
</tr>
</tbody>
</table>

RTKs and Angiogenesis

There are a group of RTKs that mediate the growth of new blood vessels (angiogenesis) in tumours. These include receptors for vascular endothelial growth factor, basic fibroblast growth factor, the angiopoietins, and others. As in tumour cells themselves, signaling through these RTKs are of prime importance in the growth and maintenance of tumour vasculature, and therapies designed to inhibit signaling through these angiogenic growth factor receptors (e.g. bevacizumab, sorafenib, sunitinib) are showing great promise in human clinical trials, and the veterinary cancer drug toceranib (Palladia®), discussed more below, which targets VEGFR2 and PDGFR as well as KIT, all 3 of which are RTKs critical for blood vessel growth.

RTKs and Veterinary Cancer

While the majority of clinical work with RTKs has focused on canine MCT, there is accumulating knowledge regarding the expression and function of RTKs in other veterinary tumours of importance. Several examples are provided below.

Recent work has demonstrated that a majority of feline vaccine-associated sarcomas (VAS) express the RTK PDGFR, the receptor for platelet-derived growth factor (PDGF). Additionally, PDGF stimulates the proliferation of feline VAS cells in culture and protects VAS cells from the antiproliferative and pro-apoptotic effects of doxorubicin. Furthermore, inhibition of PDGFR signaling with imatinib eliminates the oncogenic effects of PDGF and inhibits tumour growth in a nude mouse model of VAS. Therapy with imatinib has been pursued in a small number of tumour-bearing cats to date, and it appears to be tolerated at doses approaching those associated with antitumour activity in humans.

A variety of RTKs have been identified in canine osteosarcoma (OSA) cells, including PDGFR, HER2 (one of several receptors for epidermal growth factor), IGF-1R (the receptor for insulin-like growth factor 1), and MET (the receptor for hepatocyte growth factor). IGF-1R and MET have been shown to mediate important oncogenic functions such as proliferation, anti-apoptosis, invasion, motility and chemoresistance in canine OSA cells, and interestingly, constitutive activation of the MET receptor has been demonstrated in canine OSA as well. Furthermore, MET activity can be inhibited in canine OSA and other canine tumour cells by a small molecule in vitro. A randomized, placebo controlled trial in dogs with OSA using a somatostatin analog designed to reduce IGF-1 levels demonstrated no difference between dogs receiving chemotherapy and somatostatin analog and dogs receiving chemotherapy and placebo, however serum IGF-1 concentrations were reduced by less than half in the treated dogs. It is quite possible that more potent inhibition might result in different results.

A more complete list of RTKs identified in veterinary cancer and levels of evidence for their utility as targets for therapy is presented in Table 3.
### Table 3. Receptor Tyrosine Kinase Expression, Function and Inhibition in Veterinary Cancer.

<table>
<thead>
<tr>
<th>RTK</th>
<th>Ligand</th>
<th>Tumour Type</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT</strong></td>
<td>Stem Cell Factor</td>
<td>Canine mast cell tumour, canine hemangiosarcoma, canine melanoma</td>
<td>Expressed on most MCT / HSA: and 50% of melanomas. ~30% of MCT carry a functional activating mutation. Small molecules capable of inhibiting signaling and antitumour effects in vitro and in patients have been identified.</td>
</tr>
<tr>
<td></td>
<td>Feline mast cell tumour</td>
<td></td>
<td>Expressed on most MCT. Activating mutations have been identified.</td>
</tr>
<tr>
<td><strong>MET</strong></td>
<td>Hepatocyte Growth Factor / Scatter Factor</td>
<td>Multiple canine tumours, including osteosarcoma, melanoma, histiocytic sarcoma, mast cell tumour</td>
<td>Expressed in most tumours of the histotypes examined. Constitutive activation detected in osteosarcoma. Receptor is functional and signaling inhibitable in vitro with small molecules.</td>
</tr>
<tr>
<td><strong>IGF-1R</strong></td>
<td>Insulin-like Growth Factor-1</td>
<td>Canine osteosarcoma, melanoma</td>
<td>Expressed in most tumours of the histotypes examined. Receptor is functional and signaling inhibitable in vitro with small molecules.</td>
</tr>
<tr>
<td><strong>EGFR</strong></td>
<td>Epidermal Growth Factor, Transforming Growth Factor-alpha, others</td>
<td>Canine mammary, lung, transitional cell, and nasal carcinoma, feline oral SCC</td>
<td>Expression documented most tumours of the histotypes examined. Receptor is functional in canine mammary carcinoma and signaling inhibitable in vitro with small molecules.</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>Epidermal Growth Factor, Transforming Growth Factor-alpha, others</td>
<td>Canine and feline mammary carcinoma, canine osteosarcoma</td>
<td>Expressed in a large minority of canine and feline mammary tumours, appears overexpressed in some canine osteosarcomas. Coreceptor for EGFR so may contribute to biologic effects of EGF in mammary carcinoma.</td>
</tr>
<tr>
<td><strong>PDGFR</strong></td>
<td>Platelet-Derived Growth Factor</td>
<td>Canine osteosarcoma and hemangiosarcoma, feline vaccine-associated sarcoma</td>
<td>Expressed in canine osteosarcoma. Expressed, functional and inhibitable with small molecules in vitro and in mouse models of vaccine-associated sarcoma and HSA.</td>
</tr>
<tr>
<td><strong>VEGFR2</strong></td>
<td>Vascular Endothelial Growth Factor</td>
<td>Canine hemangiosarcoma, melanoma, nasal carcinoma Tumour vasculature</td>
<td>Expressed in some melanoma and nasal carcinomas and most HSA. Some evidence of functionality in canine HSA cells. Increased concentrations of ligand detected in serum of HSA patients.</td>
</tr>
<tr>
<td><strong>FGFR1 and 2</strong></td>
<td>Basic Fibroblast Growth Factor</td>
<td>Canine hemangiosarcoma Tumour vasculature</td>
<td>Expressed in most HSA evaluated. Evidence of functionality in canine HSA cells. Increased concentrations of ligand in urine of HSA patients.</td>
</tr>
<tr>
<td><strong>TrkA</strong></td>
<td>Nerve Growth Factor</td>
<td>Canine osteosarcoma</td>
<td>Expressed in most OSA. Blockade of TrkA induces apoptosis.</td>
</tr>
</tbody>
</table>

**Canine Mast Cell Tumour and KIT**

Perhaps the most important recent finding with potential to translate into new and exciting forms of therapy is the discovery that the majority of canine (and human) mast cell neoplasms express the tyrosine kinase growth factor receptor KIT, and a large minority of canine MCT (20-50% depending on the study) possess a mutation in the *c-kit* gene coding for the KIT protein. (KIT expression and *c-kit* mutations have also been identified in feline MCT recently). This gene codes for a transmembrane protein that serves as the receptor for the growth factor stem cell factor, important in the maturation of normal mast cells and other hematopoietic cells. Mutations can render KIT active even in the absence of bound stem cell factor. In other words, these mutations mean that the cells are receiving signals to proliferate and survive when they normally would not, leading to unchecked growth. New molecules...
have been developed that inhibit signaling through the KIT tyrosine kinase, and these compounds are able to interfere with the proliferation of canine MCT in vitro. The 2 veterinary-approved molecules in this class are toceranib (Palladia®, Pfizer) and masitinib (Masivet®/Kinavet®, AB Science).

Following encouraging in vitro and early-phase clinical studies with toceranib, a multi-center, placebo-controlled, double-blind, randomized study of toceranib was performed in dogs with recurrent or metastatic grade II or III MCT. Dogs were randomized to receive oral toceranib 3.25 mg/kg or placebo every other day for 6 weeks in the blinded phase. Thereafter, eligible dogs received open-label toceranib. The overall response rate in toceranib-treated dogs (n = 86) was 37.2% (7 complete response, 25 partial response) versus 7.9% (5 partial response) in placebo-treated dogs. Among the toceranib treated responders, the median duration of objective response and time to tumour progression was 12.0 weeks and 18.1 weeks, respectively. Interestingly, dogs whose MCT harbored activating mutations in the c-kit gene were roughly twice as likely to respond to toceranib than those with wild-type c-kit (60% vs 30%). The efficacy observed in this study led to the full approval of toceranib by the U.S. FDA.

Subsequent to FDA approval, considerable clinical experience with toceranib has been amassed by U.S. oncologists. Important observations in this post-approval phase include the high incidence of gastrointestinal toxicity in dogs treated with the label-indicated dosage and schedule: most U.S. oncologists currently utilize a dose of 2.5-2.75 mg/kg every-other-day or Monday-Wednesday-Friday, which appears well tolerated by the majority of dogs. Gastrointestinal toxicity, in the form of inappetance, weight loss, diarrhoea, and occasionally vomiting or melena, are the most common adverse effects, and are generally manageable with symptomatic therapy, drug holidays and dosage reductions as necessary. Other adverse effects reported include mild to moderate leucopenia, and occasional muscle pain or leukotrichia.

A clinical trial of similar design was recently completed with masitinib in dogs with recurrent or unresectable MCT. Masitinib was administered at a dose of 12.5 mg/kg daily. This study demonstrated significantly improved time to progression in masitinib-treated versus placebo-treated dogs, and again, response rate and outcome was improved in dogs with MCT harboring c-kit mutations. Gastrointestinal adverse effects (vomiting or diarrhoea) were most common but were mild in the vast majority of cases (usually grade 1 or 2) and self-limiting. Myelosuppression can also occur, particularly neutropenia, although in most cases this is mild. A small percentage of dogs developed a protein-losing nephropathy leading to oedema. Increases in urea and creatinine were seen in some dogs, although this was not clear if it was drug-related or not – however caution is recommended when using this drug in patients with pre-existing renal disease. Haemolytic anaemia was also seen as a rare occurrence in the study.

Practical Monitoring of patients on RTKIs

- Clinicians and owners should be vigilant to monitor patients for adverse effects, as described above. Monitoring of complete blood counts, serum biochemistry profiles and urinalysis is suggested at baseline, after 2 weeks of therapy and monthly thereafter. Dose reductions, drug holidays or supportive care, in the form of gut protectants, may be indicated.

A variety of unanswered questions exist regarding the use of RTK inhibitors such as toceranib and masitinib for the treatment of animal cancer. These include: (1) Can they be given to cats safely? The answer to this appears to be yes, but evidence of efficacy is limited to a small number of cats that have been treated with imatinib (see cat section). (2) Are there other tumours where they might be efficacious? Anecdotal or early evidence of efficacy has been reported for toceranib for the treatment of diverse diseases including multiple myeloma, soft-tissue sarcoma, metastatic osteosarcoma and carcinomas of the mammary gland, thyroid and anal sac; similarly, there are reports of antitumour responses to masitinib in dogs with T-cell lymphoma. In these other tumour types, efficacy may be as
a result of the targeting of other RTKs important in cancer, such as PDGFR or VEGFR2. (3) Are they effective for the postoperative treatment of incompletely resected or “high-risk” MCT? This has not been studied. Further complicating this question, it is not at all clear how long these drugs should be continued in the postoperative setting. (4) Can they be used together with chemotherapy or radiation therapy? This is not clear, however preliminary evidence suggests that toceranib can be combined safely with coarsely fractionated (palliative) radiation therapy, with encouraging antitumour activity. Early reports suggest additive toxicity when toceranib is combined with traditional cytotoxic chemotherapeutic agents such as VBL or CCNU, which suggest that significant dosage reductions of the cytotoxic agent may be necessary if the drugs are to be safely combined. Early abstracts suggest that masitinib/chemotherapy combinations (doxorubicin/carboplatin) may be tolerated at chemotherapy doses approaching the maximum tolerated dose. A combination of toceranib and low dose continuous (“metronomic”) cyclophosphamide has also been investigated, and tolerability of both agents at full dose appears to be excellent.

FELINE MAST CELL TUMOURS
PREVALENCE AND RISK FACTORS
Mast cell tumours (MCT) represent the second most common cutaneous tumour in cats, accounting for approximately 20% of feline cutaneous tumours in the United States. MCT appear to occur less frequently in the United Kingdom, accounting for only 8% of all cutaneous tumours. Two distinct forms of cutaneous MCT in the cat have been reported: (1) The more common “mastocytic” MCT, which can be subdivided into well-differentiated and pleomorphic subtypes and (2) The less common atypical MCT (or “histiocytic” MCT). An overall mean age of 8 to 9 years is reported for cats with MCT; however, the mastocytic and atypical forms occur at mean ages of 10 and 2.4 years respectively. Siamese cats may be predisposed to development of MCT of both histologic types, with the atypical form reported to occur primarily in young (<4 years old) Siamese cats. There does not appear to be a sex predilection.

Visceral MCT are more common in cats than in dogs, with up to 50% of MCT cases occurring in visceral sites in some series. Splenic MCT represent the most common differential diagnosis for ‘splenic disease’ in cats, accounting for 15% of submissions in a series of 455 pathologic specimens. Mean age of affected cats is approximately 10 years and no breed or sex predilection is known. Intestinal MCT is the third most common primary intestinal tumour in cats after lymphoma and adenocarcinoma. No breed or sex predilection is known. Older cats appear to be at risk with a mean age of 13 years, however cats as young as 3 years have been reported. In contrast to dogs, cats with visceral MCT disease often do not have concurrent or historical evidence of cutaneous MCT, although rarely they do occur concurrently.

The aetiology of feline MCT is unknown. A genetic predisposition has been proposed due to the high prevalence of MCT in the Siamese breed. Mutations in the KIT gene appear to be common in feline mast cell tumours (present in 67% of tumours in one study) and may play a role in oncogenesis. Mutations were identified most frequently in exons 8 and 9, (which encode the extracellular fifth immunoglobulin domain of the KIT receptor and may promote receptor dimerization and subsequent kinase activation. Other mutations have been found in exon 6 (encoding the extracellular immunoglobulin domain 4) and in exon 11, which encodes the juxtamembrane region of the receptor, similar to the site of mutations observed in canine MCT.

PATHOLOGY AND NATURAL HISTORY
Feline MCT have been classified histologically as mastocytic (with well-differentiated and pleomorphic subtypes) and atypical types. The atypical type was previously called “histiocytic” although this term is now discouraged, to avoid confusion with diseases with true histiocytic proliferations. Well-
differentiated mastocytic MCT are more common than the pleomorphic subtype. Atypical MCT are rare.

Histopathological features of the different types of Feline MCT are found in **Table 4.**

<table>
<thead>
<tr>
<th>Mastocytic well-differentiated subtype</th>
<th>Mastocytic pleomorphic subtype</th>
<th>Atypical MCT (previously known as “histiocytic”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Less common</td>
<td>Rare</td>
</tr>
<tr>
<td>Variably demarcated, unencapsulated dermal mass or masses, may invade subcutis</td>
<td>Less discrete, tend to infiltrate deeper into the dermis and subcutis</td>
<td>Granulation moderate to low. Large and polygonal to spindle shaped cells with abundant amphophilic cytoplasm. Nuclei large and vesicular, may be indented</td>
</tr>
<tr>
<td>Negligible pleomorphism. Cells resemble normal mast cells (i.e. relatively small and highly to moderately granulated)</td>
<td>Pleomorphic cells. Granulation variable. Anisocytosis, large eccentric nuclei, prominent nucleoli. Variable presence of giant cells, with multilobulated single nucleus or multinucleated</td>
<td>Low Mitotic Index</td>
</tr>
<tr>
<td>Low Mitotic Index</td>
<td>Variable Mitotic Index (low to high)</td>
<td>Low Mitotic Index</td>
</tr>
<tr>
<td>Eosinophils in 50% of cases (+)</td>
<td>Eosinophils often present (++)</td>
<td>Numerous eosinophils (+++).</td>
</tr>
<tr>
<td>+/- lymphoid aggregates</td>
<td>+/- lymphoid aggregates</td>
<td>Frequent lymphoid aggregates</td>
</tr>
</tbody>
</table>

The granules present in feline MCT stain blue with Giemsa and purple with toluidine blue. They tend to appear more eosinophilic than their canine counterparts with hematoxylin and eosin stains. Similar to dogs, the granules present in feline mast cells contain vasoactive substances such as heparin, histamine and others, also chymase and tryptase. Release of granule contents can cause clinical signs. Feline mast cells also have phagocytic capability and can endocytose erythrocytes and inflammatory cells. Immunohistochemical studies performed on feline MCT showed that all were vimentin positive and the majority were positive for α-1 antitrypsin.

The uncommon atypical (“histiocytic”) form of feline MCT can be challenging to diagnose histologically, since many of the cells lack granules and they are accompanied by eosinophilic and lymphoid infiltrates. They can be initially misdiagnosed as granulomatous nodular panniculitis or deep dermatitis. Availability of special stains and immunohistochemistry, including toluidine blue, chymase, tryptase and KIT/CD117 should help to identify the round cells present as being of mast cell origin. Spontaneous regression of these atypical (“histiocytic”) MCT has been reported in the literature, over a period of 4 to 24 months.

The majority of feline cutaneous MCT have a relatively benign clinical behaviour. Metastatic rates for cutaneous MCT in cats vary considerably, with reported rates of 0-22%. It would be beneficial to have a way of predicting which subset of cutaneous MCT is likely to behave aggressively. The Patnaik histologic grading system described for canine cutaneous MCT has provided no prognostic information for cats. Currently, mitotic index (the number of mitotic figures per 10 hpf) appears to be one of the strongest prognostic indicators, as demonstrated by several studies. It is unclear whether Ki-67 expression gives additional prognostic information over MI, since they are strongly correlated. Whether KIT expression or c-kit mutations play a role in prognosis or not requires further investigation. Up to 84% of cutaneous MCT in cats express KIT (CD117), with aberrant cytoplasmic staining in 52% - 67%. The KIT immunoreactivity score, a measure of positively staining cells and the intensity of staining, was assessed in one study – it was found to correlate with MI, Ki-67 and clinical outcome and was highest in the pleomorphic MCT.
In terms of clinical outcome, multiplicity of lesions, MI, Ki-67 index, KIT immunoreactivity score, and pleomorphic phenotype correlated with an unfavourable outcome in one study. The pleomorphic tumours in this study had significantly higher MI, Ki-67 index and KIT immunoreactivity scores than the mastocytic well-differentiated or atypical subtypes. However, in another study of 15 pleomorphic MCT, fourteen had benign behaviour and only the tumour with a high MI showed malignant behaviour, suggesting that the MI may actually be the most critical factor.

In summary, a combination of the clinical presentation, histological type of MCT and particularly the MI should be considered to try to predict the biological behaviour of feline cutaneous mast cell tumours.

With regard to visceral forms of MCT cats (i.e. splenic and intestinal), widespread dissemination and metastasis is much more common. Necropsy data on 30 cats with splenic MCT revealed dissemination in the following organs in decreasing order of frequency; liver (90%), visceral lymph nodes (73%), bone marrow (40%), lung (20%), and intestine (17%). Up to a third of cases have peritoneal and pleural effusions rich in eosinophils and mast cells. Peripheral blood mastocytosis is present in as many as 40% of cases. In one clinical report of 43 cases, 23% had bone marrow involvement. Two gross forms of splenic involvement are possible; a diffuse and smooth form and a less common nodular form. In one report, 18% of cats with cutaneous MCT went on to develop splenic disease. Interestingly, in the face of widespread metastasis, long-term survival following splenectomy is common with splenic MCT (see Treatment section). Intestinal MCT in cats is also associated with widespread dissemination and carries a poor prognosis. It more commonly involves the small intestine (equally divided between duodenum, jejunum and ileum) with colonic involvement reported in less than 15% of cases. Lesions can be solitary or multiple. Peritoneal effusion rich in mast cells can occur. Unlike splenic MCT, peripheral mastocytosis is rarely associated with intestinal MCT and only two reports of peripheral eosinophilia exist in the literature. Metastasis is common to mesenteric lymph nodes and liver, followed less commonly by spleen lung, and bone marrow. Most animals either die or are euthanized soon after diagnosis of small intestinal MCT. Histologically, mast cells from intestinal lesions appear less differentiated than those of skin tumours and cytoplasmic granules are less prominent.

An unusual presentation of intestinal feline sclerosing mast cell tumour has been reported in the literature recently. This variant has a characteristic histopathology, where the neoplastic mast cells are arranged in a trabecular pattern in amongst moderate to dense stromal collagen (sclerosis) with a moderate to marked eosinophilic infiltrate. Ulceration is common (58% of cases). The disease course is aggressive, with metastasis to the lymph node and liver present in two thirds of cases assessed and most cats died within 2 months of the diagnosis. Care must be taken to differentiate this type of tumour from other lesions with a similar morphologic appearance, such as feline gastrointestinal eosinophilic fibroplasia, or septic abscesses with prominent eosinophil infiltration. Immunohistochemical techniques may be necessary to confirm the diagnosis.

A cranial mediastinal form of MCT in cats has also been described.

**HISTORY AND CLINICAL SIGNS**

Cutaneous tumours: The typical feline cutaneous MCT is a solitary, raised, firm, well circumscribed, hairless, dermal nodule between 0.5 and 3 cm in diameter. They are often white in appearance, although a pink erythematous form is occasionally encountered. Approximately 20% are multiple, although one series from the United Kingdom reported multiple lesions in the majority of cases. Superficial ulceration is present in approximately a quarter of cases. Two other clinical forms have been described; one is a flat pruritic plaque-like lesion similar in appearance to eosinophilic plaques, and the other discrete subcutaneous nodules.
The head and neck are the most common site for MCT in the cat, followed by the trunk, limbs and miscellaneous sites. Those on the head often involve the pinnae near the base of the ear. They rarely occur in the oral cavity. Intermittent pruritus and erythema are common, and self-trauma or vascular compromise may result in ulceration. Darier’s sign, the erythema and wheal formation following mechanical manipulation of the tumour, has been reported in cats. Affected cats are usually otherwise healthy.

The atypical (previously called histiocytic) spontaneously regressing form of cutaneous MCT are usually multiple, non-pruritic, firm, hairless, pink and sometimes ulcerated subcutaneous nodules. Affected animals are otherwise healthy.

Cats with disseminated forms of MCT may present with signs of systemic illness. Depression, anorexia, weight loss, and intermittent vomiting are most commonly associated with splenic and intestinal MCT. Abdominal palpation reveals massive splenomegaly in the majority of cases, and occasionally peritoneal effusion is evident with splenic MCT. Intestinal MCT can often be palpated as well. Diarrhoea with or without bloody stools or melaena is commonly seen with the intestinal form, and fever may be present. Affected cats usually have been ill for several months. Signs related to release of vasoactive components of mast cell granules, including gastrointestinal ulceration, uncontrollable hemorrhage, altered vascular smooth muscle tone, hypotensive shock and laboured breathing due to bronchoconstriction are more likely to be observed with systemic forms. These signs are often episodic in nature. Labored breathing may also occur secondary to pleural effusion or anaemia, both of which are present in approximately one-third of disseminated MCT in cats.

**DIAGNOSTIC TECHNIQUES AND WORK-UP**

The diagnosis and staging of MCT in cats is similar to that in dogs. Fine-needle aspiration (FNA) cytology should be performed for cutaneous lesions and is usually diagnostic in the mastocytic form of the disease. Tissue biopsy and histologic assessment (+/- special stains) is typically required for the atypical or “histiocytic” form of MCT.

Although metastasis is uncommon in feline cutaneous MCT, local lymph nodes should always be palpated and aspirated if enlarged.

For suspected disseminated or visceral disease, a full CBC and serum biochemistry profile should be performed. One third of cats with visceral disease are anaemic, and cases may show signs of bone marrow involvement. Buffy coat smears often show mastocytosis. Peripheral mastocytosis can be striking; peripheral mast cell counts up to 32,000 cells/µL have been reported. Unlike the splenic form, intestinal MCT is not commonly associated with peripheral mastocytosis, however eosinophilia has been reported. Bone marrow aspiration may be considered but may not affect treatment. Up to 50% of cats with splenic MCT have evidence of bone marrow and buffy coat involvement. If abdominal surgery is contemplated, coagulation times (APTT and PT) should be assessed. In one report of 43 cats with splenic MCT, 90% had laboratory evidence of coagulation abnormalities. Hyperglobulinemia has also been reported in cats with splenic MCT, the cause of which remains unknown.

In cases where disseminated disease is suspected e.g. with splenic lesions or intestinal masses, further investigations are indicated. Abdominal ultrasound should be performed to confirm the location of the mass and to determine the extent of disease. Ultrasound-guided FNAs should be taken from splenic or intestinal lesions, although intestinal aspirates may not yield a diagnosis. FNAs of other abnormal organs / lymph nodes should be taken. Differential diagnoses for splenomegaly in cats include lymphoma, myeloproliferative disease, accessory spleen, haemangiosarcoma, hyperplastic nodules and splenitis. The two most common differential diagnoses for intestinal masses...
in aged cats are lymphoma and adenocarcinoma. If cytology from FNAs do not yield a diagnosis, an exploratory laparotomy and biopsy may be required.

Thoracic radiographs may also be useful to assess for distant metastasis or effusion. Thoracic or abdominal effusions may present in up to one third of cats with disseminated / visceral disease. Cytology following thoraco- or abdominocentesis may reveal neoplastic mast cells.

**TREATMENT AND PROGNOSIS**

**Cutaneous tumours**

Surgery is the treatment of choice for the mastocytic form of cutaneous MCT in the cat. As previously discussed, most are behaviorally benign and wide surgical margins may not be as critical as in the dog. This is fortunate, as most occur on the head where such margins would be difficult to achieve. Frequency of local recurrence and systemic spread vary widely in the literature. Local recurrence rates of 0 to 24% have been reported following surgical excision. Recurrence, should it occur, is usually noted within 6 months. Even with dirty margins, recurrence does not necessarily occur. Frequency of systemic spread following surgical excision varies from 0 to 22%. For pleomorphic mastocytic tumours, a more aggressive approach similar to that utilized for canine MCT may be prudent (particularly if the MI is high), as higher rates of recurrence and metastasis can be associated with this type. For the atypical (“histiocytic”) form of MCT in young cats with multiple masses, following biopsy confirmation, conservative resection or a “wait and see” approach may be taken, as the majority are reported to spontaneously regress.

Strontium plesiotherapy has also been used for feline cutaneous MCT with good results, with only 3% recurrence in a study with 35 cats. For cats with numerous skin lesions, or non-resectable lesions (e.g. diffuse infiltrative nature) chemotherapy may be considered – see below.

The prognosis for cutaneous MCT can be very good, as the majority are behaviourally benign. Cats with tumours confined to the skin are likely to survive significantly longer than those with visceral or lymph node tumours. Cats with multiple cutaneous tumours (>5) had a significantly poorer prognosis (MST 375 d, range 3-994 d) than those with single tumours (MST not reached) in one study. This may relate to the feasibility of performing surgery. Pathological features, particularly the type of MCT and mitotic index, should be borne in mind when considering prognosis (see pathology section).

**Splenic MCT**

Cats with splenic MCT will usually benefit from splenectomy. Surprisingly, even in the face of significant bone marrow and peripheral blood involvement, long-term survival with good quality of life is the norm following splenectomy, with median survival times from 12 to 19 months reported. Anorexia, significant weight loss, and male sex have been associated with a worse prognosis. Frequent re-evaluation and buffy coat smears are used to follow response in such cases. Rarely does the peripheral mastocytosis resolve, but it will often significantly decline and its subsequent rise can serve as a marker of progression. The role of chemotherapy following splenectomy is still not clear. Adjunctive treatment with combination chemotherapy protocols including prednisone, vincristine, cyclophosphamide, and methotrexate have been attempted in a limited number of cases but do not appear to increase survival times. The role of adjuvant lomustine or vinblastine in cats following splenectomy is currently being evaluated.

**Intestinal tumours**

The intestinal form of feline MCT carries a poor prognosis. Metastasis at the time of diagnosis is common and most cats either die or are euthanased soon after. If surgery is possible, wide surgical margins, including 5 to 10 cm of normal bowel on either side of the lesion are recommended as tumour often extends histologically well beyond visible gross disease. In the sclerosing form of
intestinal MCT, the majority (23/25 cats) were dead within 2 months of the diagnosis. One cat survived >4.5 years with surgery and vinblastine chemotherapy. It seems reasonable that adjuvant chemotherapy, should be considered in cases of feline intestinal MCT, once the laparotomy wound has healed.

**Chemotherapy for Feline MCT**

Chemotherapy may be indicated for patients with numerous skin lesions, unresectable disease, recurrent disease or disseminated disease.

- Lomustine at 50-60 mg/m² every 3-6 weeks was reported to produce a response in 50% of cats (n=38) with measurable disease (18% CR, 32% PR) with a median duration of 168 days (range 25-727 d). Adverse effects include neutropenia and thrombocytopenia, both of which can be delayed and prolonged. CBCs should ideally be measured weekly after the first dose and prior to subsequent doses. Hepatic or renal adverse effects do not appear to be common but periodic monitoring is prudent. Capsules may need to be reformulated into a suitable size for cats by a compounding pharmacy.

- Prednisolone e.g. 40 mg/m² for 7d then 20 mg/m² every other day can be used alongside lomustine. This can also be used as a single agent and may help reduce inflammation. Response to steroids in cats with the histiocytic form is equivocal.

Other drugs have been used:

- Vinblastine at 2 mg/m² +/- prednisolone (e.g. 40 mg/m² for a week then 20 mg/m² every other day).
- Chlorambucil 20 mg/m² every 2 weeks with prednisolone at 40 mg/m² for a week then 20 mg/m² every other day
- Cyclophosphamide and prednisolone
- Imatinib mesylate has been reported in 11 cats at 10 mg/kg daily. (Of 9 cats with known c-kit mutations, CR=2, PR=6, NR=1, of 2 cats with no c-kit mutations, 1=PR, 1=NR. 4 cats received concurrent medication (prednisolone, vinblastine or lomustine).

Ancillary drugs to combat the effect of vasoactive amines (see discussion under canine MCT) may be indicated alongside systemic chemotherapy e.g. chlorphenamine, famotidine, sucralfate.

**SELECTED REFERENCES**


Cooper M, Tsai X, Bennett P. Combination CCNU and vinblastine chemotherapy for canine mast cell tumours: 57 cases. Vet Comp Oncol 7: 196-206, 2009.


