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## **CANINE MAST CELL TUMOURS...DO I NEED TO DO ANYTHING ELSE?**

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Canine mast cell tumours (MCT) vary greatly, and no prediction can be made for their behavior on clinical appearance alone. Important prognostic information can be gained from histologic grading and assessment of surgical margins. Surgical excision is indicated if the tumour is solitary and is the treatment of choice for grade 1 and 2 MCT. Excision should include a minimum 2cm margin around the borders of the tumour and one fascial plane below. Incomplete excision should be followed by further surgery, or by radiation therapy; both provide excellent long-term local control. Grade 3 or metastatic MCT are best treated by chemotherapy and/or palliative therapy. Active chemotherapy agents include vinblastine and lomustine (CCNU). Recent identification of mutations in tyrosine kinase receptors on MCT cells implies an exciting new therapeutic role for drugs that target these receptors.

In dogs, mast cell tumours (MCTs) are most commonly found in the cutaneous tissue. In most dogs, tumours are solitary, but in about 6%, the tumours are multiple. Tumours usually occur in older dogs (mean age = 9 years) with no sex predilection. Boxers, Rhodesian ridgebacks, pugs, Boston terriers, pit-bull terriers and Weimaraners are at high risk (4 to 8 times more than the population) for developing MCTs. Shar-Peis, particularly young dogs, are predisposed to developing MCT, and these tumours are often poorly differentiated and aggressive biologically.

It is uncommon to diagnose MCTs without skin involvement in dogs. Mast cell tumours vary greatly in appearance, and no estimate of their malignancy or prediction of their behavior can be made on clinical appearance alone. Some MCTs may be present for months to years before rapidly disseminating; others act aggressively from the beginning. Approximately 6% of dogs will develop multiple cutaneous MCT. Occasionally, mechanical manipulation during examination of this tumour causes degranulation of mast cells, producing erythema and wheal formations. This phenomenon has been observed in both dogs and cats (the "Darier's sign") and is considered of diagnostic significance. Owners may report that the tumour enlarges rapidly and then diminishes in size over a period of about 24 hours. Such a history should increase the clinician's suspicion of mast cell tumour.

The clinical appearance of MCTs in dogs may vary widely but diagnosis is relatively easy using aspiration cytology. Presurgical aspiration of these tumours provides a cytology specimen characterized by *round cells* that may have well-stained and large cytoplasmic granules (well-differentiated) or that may be more anaplastic with small, poorly staining cytoplasmic granules. Eosinophils are often seen in aspirates of MCTs because of eosinophil chemotaxis to histamine release. Diagnosis of MCT often can be made by fine-needle aspiration cytology; but excisional biopsy is required for accurate histologic grading of the tumour. Histopathologic grading of the tumour has been correlated with both recurrence and survival.

All dogs with MCTs should be staged to determine the extent of their disease. This is especially important for dogs being considered for aggressive surgery such as amputation, or radiation therapy. To establish the stage of a dog with a cutaneous MCT, the following information is needed:

1. *Complete Blood Count (CBC), Serum Chemistry Profile and Urinalysis*
2. *Lymph Node Aspirates*

The clinician should perform fine-needle aspiration of the regional lymph node if the node is enlarged. The presence of clusters of mast cells (and eosinophils) is an indication that the MCT may no longer be confined to the primary site. Mast cells may infiltrate a regional lymph node in a dog with a MCT as an inflammatory response to the tumour, therefore a suspicious cytology result should be confirmed by biopsy.

### 3. Radiographs and Ultrasonography

Splenomegaly or hepatomegaly may indicate spread of MCTs systemically. Pulmonary metastasis of MCTs is rare. Ultrasonography is most useful for staging a dog with MCT if used in conjunction with histopathology or cytology.

### 4. Bone Marrow Aspirates

The presence of >1% mast cells indicates systemic spread of the neoplasm. In a recent report 4.5% of dogs with cutaneous MCT had either >1% or abnormal mast cells in a bone marrow aspirate.

### 5. Miscellaneous Tests

Fecal occult blood tests may be useful in evaluating patients with mast cell disease. In many cases, feces may contain small amounts of blood that are insufficient to produce melena. Evidence of gastrointestinal bleeding in a patient with a MCT should prompt the clinician to treat with medications that block the effects of mast cell hyperhistaminemia (i.e., H<sub>2</sub> blockers, such as cimetidine, ranitidine, famotidine).

### 6. Buffy Coat Smears

Care must be exercised in interpreting buffy coat smears, because mastocytomia has been reported in a variety of canine acute inflammatory diseases (see below). For this reason, most oncologists now feel that this test has limited applicability to staging of dogs with MCT. We no longer recommend it as part of staging for MCT.

**Prognostic Factors:** Recent clinical research has led to the identification of prognostic factors for dogs undergoing therapy with surgery and radiation therapy, and this same research has led to changes in thinking about other previously well-accepted prognostic factors.

**Gender:** male dogs had a worse prognosis after chemotherapy treatment for MCT.

**Age:** dogs older than 8 years were nearly 3 times more likely to die of their disease after treatment for MCT.

**Growth Rate:** Dogs with tumours that grow at a rate greater than 1 cm per week appear to have a worse prognosis, in an early study of dogs treated with surgery alone.

**Tumour Grade:** Recent studies using aggressive surgical technique, and histology to examine margins (rather than the surgeon's clinical impression), has shown that dogs with grade 2 MCT have a *much lower rate of local recurrence and longer survival rates* than was previously believed. Nonetheless grading is still an important prognostic factor. Grade 3 tumours are more likely to be incompletely excised, more likely to metastasize and nearly 4 times more likely to result in death than tumours of lower grades.

**Surgical Margins:** The completeness of excision (i.e., whether the surgical margins are "dirty") is an important prognostic factor and also important in determining if further surgery or adjunctive radiation therapy is needed. There is often disparity between the surgeon's assessment of margins and those assessed by histopathology. In one study 22 of 59 tumours thought to have been excised widely had either questionable (10) or incomplete (12) excision based on histological examination.

Dogs with incomplete excisions are more likely to develop metastatic disease. Because of this finding, and because tumour recurrence is still more common following incomplete excision, the clinician is counseled to obtain clear surgical margins wherever possible, and not to rely on a marginal excision.

**Tumour stage:** Dogs with lymph node metastases are nearly 8 times as likely to die of MCT. A potential problem with staging is that small numbers of mast cells may be found in the circulation, spleen, liver and bone marrow, so the significance of such a finding is unclear. In one study the presence of small numbers of mast cells in these locations did not seem to influence survival in dogs with grade 2 MCTs. Mast cells may infiltrate a regional lymph node in a dog with a MCT as an inflammatory response to the tumour, therefore a suspicious cytology result should be confirmed by biopsy. Although it is strictly considered grade 3, the presence of multiple MCTs does not necessarily confer a worse prognosis.

## **Treatment**

Control of canine MCTs involves the use of surgery, chemotherapy, or radiation therapy, either individually or in combination.

### *Surgery*

Surgical excision is indicated if the tumour is solitary and evidence of lymph node involvement or systemic spread is lacking. Excision should be wide and deep to a minimum margin of 2-3 cm around the perceived borders of the tumour and one fascial plane below. With this approach, recurrence of grade 1 and grade 2 MCTs is very low. A recent study examined the completeness of surgical excision at margins 1cm, 2cm and 3cm from the edges of grade 1 and 2 MCT. All grade 1 tumours were excised 1 cm from the tumour borders, while only 75% of grade 2 tumours were completely excised at the same distance.

As previously stated, surgical excision should be aggressive. All excised tissue should be examined histologically for completeness of tumour excision. Extension of the tumour beyond the surgical borders or a report of "close" margins should prompt wider excision if this is possible. A second excision should include the previous excision site plus lateral margins of 2 cm and additional deep tissue. If the tumour cannot be completely excised due to tumour location or other factors, or if it is a grade 3 MCT, further therapy is indicated. The animal should be evaluated for radiation therapy, if available. Chemotherapy may be considered if staging disclosed metastases, or if the MCT is grade 3.

### *Radiation Therapy*

Mast cell tumours are quite sensitive to the effects of radiation therapy, even at moderate doses. Dogs that have no measurable evidence of disease after surgical removal of MCTs but which had incomplete excision on histologic examination of excised tissues has significantly longer tumour control and survival following radiation therapy than other dogs. Thus, post-surgical radiation therapy for incompletely excised tumours seems beneficial. Mast cell tumours of the extremities often present the greatest challenge for complete surgical excision. For well- or moderately differentiated tumours in these locations, combined modalities of less aggressive surgical "debulking" followed by radiation therapy may be a more acceptable treatment—both functionally and cosmetically.

Palliative radiation therapy may relieve symptoms of extensive or systemic disease. When the tumour is poorly differentiated or metastasis is already confirmed, high-dose intermittent radiation treatments may improve the quality of life by stopping bleeding or reducing the size of a bulky or irritating tumour. In these cases, a fully fractionated course would be costly and reduce the amount of time spent by owners with the dog. A coarsely

fractionated series of treatments may provide relief from symptoms, although it will not increase life span. Systemic therapy, as outlined later, can also be considered.

### *Systemic Therapy*

Metastatic disease was found to occur more frequently in dogs that had grade 3 MCT, and in dogs that had incomplete surgical excision of their cutaneous tumour. When MCTs have metastasized or spread systemically, localized therapies, such as surgery or radiation, are appropriate only as palliation for discomfort or mechanical obstruction. For these dogs, systemic therapy is required.

**Corticosteroids** are primarily palliative, but some long-term responses do occur. Oral prednisone is given as long as the tumour does not progress. Anecdotally, dogs that are tumour-free after six months have a lower incidence of recurrence; therefore, therapy is usually discontinued at this time.

**Vinblastine** and prednisone were used to treat MCTs in one study. The response rate in dogs with measurable disease was 47%, there were 5 complete responses and 2 partial responses. The median response duration was 5 months (1 to >22 months). Dogs with lower grade tumours seemed to respond better. Vinblastine is myelosuppressive, and a CBC should be performed weekly and prior to administering the drug.

**CCNU (Lomustine)** was given to 19 dogs. One had a complete response for 15 months, and 7 had a partial response for an average of 3 months (1 to 9 months). CCNU can be combined with prednisone. If using CCNU, monitor CBC (especially platelet count) and liver enzymes, and discontinue if thrombocytopenia or increased liver enzymes occur.

**Vincristine** was found to be an inactive agent for the treatment of MCT and often causes severe gastrointestinal toxicity. It is not recommended as a first-line chemotherapy agent for the treatment of MCT.

### *Novel Therapies*

Mutations in the proto-oncogene c-kit were shown to lead to constitutive phosphorylation of the gene product, and are believed to be important in the development and progression of canine MCT.<sup>65</sup> There is no evidence that such mutations are breed associated. Abnormalities in c-kit are more common in grade 2 and grade 3 tumours than in grade 1 MCT implying a role in biologic behavior of MCT in dogs. Mutations in one study were seen in more than one-third of dogs with grade 2 or grade 3 MCT.

The therapeutic implication of such a finding is that kinase inhibitors may be useful, such as imatinib mesylate (Gleevec) which has been reported to cause clinical remissions in human patients with similar c-kit mutations. Gleevec has anecdotally caused serious morbidity and mortality when used in the dog limiting its clinical usefulness for veterinary medicine. However, clinical trials using drugs with a similar mode of action are underway in canine patients with preliminary encouraging results with one such drug (SU11654).

### *Palliation of Paraneoplastic Symptoms*

Ancillary drug therapy is important with canine MCTs. Animals with mastocytosis or bulky mast cell disease should receive H<sub>2</sub> antagonists, as rapid degranulation of neoplastic mast cells may follow surgery or chemotherapy. Elevated systemic histamine levels may also be seen with recurrent disease. The objective of the therapy is to prevent gastrointestinal ulceration associated with elevated levels of histamine and to treat ulcers already present. This is most likely to occur in dogs with larger, bulky disease, with recurrence of cutaneous

disease, or with systemic spread of MCT. Cimetidine reduces gastric acid production by competitive inhibition of the action of histamine on H<sub>2</sub> receptors of the gastric parietal cells. Ranitidine or famotidine, H<sub>2</sub> antagonists that require less frequent administration, may be used for a similar effect. Omeprazole, which inhibits gastric acid production by the gastric parietal cells through proton pump inhibition, may also be used. Dogs with evidence of gastrointestinal ulceration and bleeding may benefit from sucralfate therapy. Sucralfate reacts with stomach acid to form a highly condensed, viscous, adherent, paste-like substance that binds to the surface of both gastric and duodenal ulcers. The barrier formed protects the ulcer from potential ulcerogenic properties of pepsin, acid, and bile, allowing the ulcer to heal. Such H<sub>1</sub> antagonists as diphenhydramine should be considered for use along with cimetidine before and after surgical removal of canine MCTs to help prevent the negative effects of local histamine release on fibroplasia and wound healing. A second generation H<sub>1</sub> antagonist, loratadine, has been shown to be very effective at inhibiting histamine release by blocking degranulation from normal canine mast cells, and therefore may be a good choice for palliation of dogs with MCT.